CHILDREN ARE NOT MINIATURE ADULTS: KEY ISSUES IN MEDICINES FOR CHILDREN

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I thank the Faculty of Medicine, University of Jaffna for giving me the privilege of delivering the Dr. Sivapathasundaram Memorial Lecture. Unlike many other memorial lectures, this lecture is dedicated to one, who had his date with destiny, at a relatively young age and in a violent matter. I regret that I only had few opportunities to see him in person as he met his untimely death within a couple of years of my admission to the Jaffna Medical Faculty. However, even after a quarter decade, his memories still stay with me, and I am honoured to deliver his memorial lecture. The honour is doubled as the invitation came from the Dean of the Faculty of Medicine, University of Jaffna, the institution to which I have the greatest respect.

Dr. Sivapathasundaram was born to Somasundarampillai Arunasalam (who was a school master) and Valliammai on the 23rd of November 1939, at Puloly, Point Pedro and was named after his grand uncle, the Late S Sivapathasundaram, a former Principal of Victoria College and popularly known as "Saiva Periyar". He had two brothers and three sisters, one brother Mr. A Somasundarampillai was a well known and successful accountant, and the other, Mr. A Rajasundaram, was a successful Engineer. Of three sisters, the eldest is a house wife, the other, Dr Mrs. Maheswary, was the Head of the Tamil Department of University of Peradeniya. The youngest sister retired as a Graduate Teacher.

Dr. Sivapathasundaram had his primary education at Vadamaradchi Hindu Girls' College and Secondary Education at

Hartley. He obtained a number of prizes for oratory and took part in Dramatics also. His interests in dramatics was not confined to College. His skills were portrayed in Radio Ceylon with Dr. Sivathamby and later with others. He also inspired the Jaffna Hospital Staff Welfare Society to produce drama, he playing the chiefrole.

He obtained the Diploma in Child Health (Sri Lanka) in 1970, proceeded to London afterwards and obtained the Diploma in Child Health (London) in 1975 and the Membership of the Royal College of Physicians in 1977. During his career, he served in Ratnapura, Balangoda, Ragama, Kuliyapitiya, Matara, Lady Ridgeway Hospital for Children, Colombo, and Chilaw before assuming duties as Consultant Paediatrician at Base Hospital Point Pedro on 1st of June 1974. Having served nine years at Point Pedro, he was appointed as a Consultant Paediatrician to the Teaching General Hospital, Jaffna in February 1983. Sad to say, his period of service was interrupted by his exemplary qualities, paving the way for his demise.

As a Paediatrician, he was punctual disciplined, meticulous, kind and left no stone unturned in the treatment of his patients. His clinical skill was good and his interests in his patient were such that, he would even go to the operation theatre to know all about the patients he referred to the Surgeons. His dealings with Colleagues, junior doctors, medical students and other staff were very friendly but if the occasion demanded, he would be stern with the staff for the sake of the patients. He treated all patients alike and followed them up keenly. He took an interest in the welfare of the Hospital and according to his colleagues that he always comes out with meaningful suggestions at staff conferences. During his time, he fought for the construction of a 1200 beds New Teaching Hospital in Jaffna. He always stood up against injustice and unfairness.

He took a great interest in the activities of the Jaffna Medical Association, often taking part in the clinical demonstrations and discussions. One could then discern the ample knowledge and clarity of thought, he had. This was a great boon for the students who clerked under him. He was elected as the Secretary of the Jaffna Medical Association in July 1987 and functioned efficiently for the short period before his demise. He was also Secretary of the Parents Teachers Association of Vembadi Girls College and I was told that he never missed a meeting. Such was his interest in anything he undertook. He was a good chess player and used to beat many of his opponents.

As an individual, he was a highly religious person, who performed poojas every morning and evening. He was a highly principled, honest, sincere and forthright person, never afraid to express his opinion. He was energetic and always ready to fight for a cause. It was these qualities that earned him displeasure and criticism from just a few but he was untroubled by these comments because he knew that such baseless and false criticisms were made to stop him from his fights for justice. He was always ready to help anyone in distress or need.

As a loving husband and father of four daughters, he discharged his family responsibility to their entire satisfaction. His tender loving care kept them happy. His wife Mangaleswary comes of an educated family. Her father is a retired Principal of Arunodaya College, Alaveddy. She was always a source of inspiration, help and support to him in all his endeavours. We have lost such a great personality but I am sure his grateful patients, their parents and the community will remember him forever.

Ladies and Gentlemen, I have tried to pay a fitting tribute to Dr Sivapathasundaram the last few minutes, but as a person who was interested in the wellbeing of children, there is no better, tribute I can pay, than by dedicating, my lecture today on "Children are not miniature adults: Key issues in medicines for children" to this great person.

Medicines for children are not different from adult medicines. Medicines are the same, but children are not small adults, their bodies respond to medicines differently. They need medicines tailored to their age, body weight and physiological condition (1).

Almost 100 years ago, Dr. Abraham Jacobi (1830-1919), the father of American paediatrics, has argued that "Paediatrics does not deal with miniature men and women, with reduced doses and the same class of disease in smaller bodies, but has its own independent range and horizon" (2).

In the first part of my lecture, let me explain to you, why medicines for children have their own independent range and horizon.

1. Pharmacokinetic differences:

For a medicine to bring about its therapeutic effects, it has to be absorbed from the site of administration and delivered to the target sites. This process is known as pharmacokinetics: In simple terms, it is "What the body does to medicines?" In technical terms, pharmacokinetics is defined as "*the process of the uptake of medicines by the body, the biotransformation they undergo, the distribution of the medicines and their metabolites in the tissues, and the elimination of the medicines and their metabolites from the body over a period of time*" (3). In other words, it is the branch

of pharmacology concerned with the mathematical description of the biological rate processes by which medicine concentrations are altered in the body. These biological rate processes include absorption, distribution, metabolism and excretion of medicines.

Children, especially, newborns, both preterm and term, infants and toddlers handle medicines differently from adults chiefly due to ongoing developmental changes in the gastrointestinal tract, differences in the proportion of body fat, protein and extracellular water content and immature liver and kidney functions. These pharmacokinetic differences influence the efficacy, toxicity and dosing regimens of medicines used in children (4). For example, gentamicin, an antibacterial agent, which is entirely excreted by kidney, has a plasma elimination half life of 18 hours in preterm newborns as opposed to 2 hours in adults.

2. Pharmacodynamic differences:

After reaching the target sites, medicine has to mediate cellular events to bring about its therapeutic effects. This process is known as pharmacodynamics: In simple terms, it is "What the medicine does to the body?" In technical terms, pharmacodynamics is defined as "*the study of pharmacological actions on living systems, including the reactions with and binding to cell constituents, and the biochemical and physiological consequences of these actions" (3).* In other words, it is the branch of pharmacology concerned with the biochemical and physiological effects of medicines and the mechanisms of their actions.

Although a great deal is known about pharmacokinetic changes during development, information regarding developmental changes in pharmacodynamics is limited. Yet, medicine targets

inside the body such as receptors, transporters and channels, are also certainly subjected to the similar developmental processes. These pharmacodynamic differences influence the actions and toxicity of medicines used in children. For example, opioids are strong analgesics. Their main therapeutic effect is pain relief. But they are known to cause serious adverse effects on cardiovascular and respiratory systems. Both of their therapeutic and adverse effects are brought about by opioids acting centrally on their receptors in the brain. However,earlier development of opioid receptors specifically in the medulla and pons, where respiratory and cardiovascular centres are located, than in other parts of the brain, is responsible for higher incidence of opioid-related respiratory depression and bradycardia associated with insufficient pain relief in newborns who receive opioids (4).

3. Effects of medicines on growing tissues:

Thirdly, unlike adults, children continue to grow and develop. Hence medicines can adversely influence g**rowth potential and development** in children (5, 6). For example, the use of high doses (more than 400 micrograms per day) of inhaled corticosteroids in the treatment of asthma has been associated with a significant reduction in growth rate, when monitored in children aged 1-15 years, over a 4-year period (7). The message to doctors and parents is NOT to stop the use of inhaled corticosteroids for asthma prophylaxisin children, but to minimise the dose to the lowest effective dose and to monitor the growth velocity. Doctors should also make certain that the child is using the metered-dose inhaler properly as wrong technique leads to high systemic availability of corticosteroids due to increased swallowing (4). "There are no safe medicines - There are only safe doctors".

4. Specific diseases in children:

Fourthly, specific diseases occurring in the growing and maturing children which are not seen in adults expose the children to medicines which are either not or poorly used in adults. Examples include disorders during new-born and adolescent period. Medicines for these disorders have no adult data to extrapolate prompting the need for paediatric studies. Owing to the difficulties in paediatric clinical trials which we will see later, many medicines for these disorders have limited evidence on their efficacy and safety.

5. Adverse drug reactions specific to children:

The World Health Organization defines an adverse drug reaction as "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man" (8). There are several well-documented examples of adverse drug reactions occurring in children which are either not seen or seen less frequently in adults. For example, aspirin, which is indicated for many ailments in adults, is contraindicated in children for relief of fever or pain as it causes Reyes syndrome, a rare form of liver disorder, only in children (9).

6. Inability to express:

Infants and young children's inability to express their problems make adverse drug reactions like drowsiness or visual disturbances remain unnoticed for a long time. Not only that, even,beneficial response to medicines in children also had to come from parental observation, examination findings and investigations. A word of caution about parental observation: Yes, unlike adults children have parents as guardians. Parents can be an asset to doctors caring for children, at the same time, "super-parents" with "over- parenting" can mislead the doctors. With "super- parents", parental observation can be unreliable and mis-informative.

7. Adverse event following immunisation (AEFI):

Adverse event following immunisation is "any untoward medical occurrence which follows immunisation and which does not necessarily have a causal relationship with the usage of vaccine" (10). It is primarily an iatrogenic disease of children as immunisation programmes generally target children. The World Health Organization has a separate programme named as "GlobalVaccine Safety" (GVS) to strengthen vaccine safety activities in children globally.

Apart from the above issues which are inherent to children, there are some major external issues as well to substantiate my claim that medicines for children have their own range and horizon.

1. Inadequate clinical trial data leading to off label use of medicines:

Marketing authorisation for a new medicine is given only after the Regulatory authorities evaluating its clinical trial data on safety, efficacy and quality. The term clinical trial has been defined by various organizations. There are inter-definition differences depending on the purpose of definition. The World Health Organization defines clinical trial as "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, devices, behavioural treatments, process of care changes" (11). However, I have taken the definition by the "International conference on harmonization of technical requirements for registration of pharmaceuticals for human use" for the purpose of this lecture. Clinical trial is "any investigation in human subjects intended to discover or verify the clinical,

pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy (12).

Most medicines given to adults had gone through this rigorous process, but unfortunately many marketed medicines that are commonly used, or could potentially be used in children, have not been studied in the relevant age (13). Many reasons such as (i) high development cost(ii) limited profit margin in paediatric market, (iii) limited number of eligible trial subjects as many paediatric diseases are relatively rare (iv) difficulty in recruiting children for clinical trials, (v) ethical hurdles including the difficulties of obtaining informed consent (vi) high regulatory requirements (vii) technical obstacles, for example need for microassays, as only small volumes of samples (e.g.; blood) would be available from children, (viii) need for non-invasiveness and (viii) difficulty in predicting long term effectsduring the maturation process put off pharmaceutical industries from performing clinical trials in children (4, 14). In 2005, it was reported that the average cost to develop a new medicine was a staggering 1.3 billion US dollars (15). It also has been reported that the median cost of completing a pharmacokinetic trial in children was about 862, 000 US dollars and performing safety and efficacy trials was about 4.3 million US dollars (16).

Owing to these constraints, pharmaceutical industries do not seek a licence for paediatric use. Hence medicines were being approved with paediatric disclaimer such as "use is not recommended in children", "paediatric dose is not known" and

"manufacturers do not recommend paediatric use, etc." This prompted, Dr Harry Shirkey, in 1968, to coin the term "therapeutic orphans" for children exposing this habit of wide use of paediatric disclaimer clause in medicine labels in USA (17). In fact, around 80% of the medicines approved by the Food and Drug Administration (FDA) between 1965 and 1995 did not have paediatric labelling (18). This inevitably leads to "off label" use of medicines in children. A paediatric label "testifies to carefully reviewed clinical trial data that offer substantial evidence to support paediatric indications for which the medicine has approved use" (19).Off label use is "use of licensed medicines in a dose, age group, or by route or for an indication not keeping with the product license specification" (20).

Despite the recently introduced legislations by the European Medicines Agency and FDA to stimulate the pharmaceutical industry to investigate, the pharmacological effect and safety of both new and existing medicines in children (21,22), the situation in the ground level has not changed with about 50-90% of prescriptions for children reported to be off label (23, 24). This is unavoidable because by failing to prescribe off label, we unintentionally deny the benefits of those medicines to children.

2. Lack of suitable formulations leading to use of manipulated adult formulations:

Let us now focus on formulation of medicines. Formulation or dosage form is the physical form in which a medicine is produced and dispensed, such as a tablet, a capsule, or an injectable. The experience, globally, is that existing paediatric formulations are not optimal when it comes to dosing, dispensing, and administering to children (25). This is more of a problem with oral formulations as young children cannot swallow tablets.

Forcing very small children to swallow large tablets may cause choking and asphyxiation. Four small children died from choking on albendazole tablets during a deworming campaign in Ethiopia in 2007 (4).

Traditionally, liquid preparations namely suspension, syrupand drops had remained the recommended oral formulations for young children. However, several problems are documented with the use of liquid formulations, especially in developing countries (25-28). I am listing the key problems: (i) climate combined with problems of transport make logistics and storage of liquid medicines a real challenge, (ii) high humidity, particularly in combination with high temperature, affects the quality of liquid medicines (iii) poor access to clean water makes reconstitution of suspension a real challenge to many families, (iv) lack of access to electricity and non availability of domestic refrigerators in many families lead to improper use of liquid medicines, and (v) liquid medicines demand high development, storage and transport cost making them more expensive per treatment dosage than tablets.

These problems with liquid formulations formed the basis for the current recommendation by the World Health Organization: In 2008, an Informal Expert Meeting on Dosage Forms of Medicines for Children, at the WHO Headquarters, Geneva, Switzerland, recommended a shift from the traditional concept of liquid paediatric formulations to flexible solid dosage forms such as tablets that are oro-dispersible and or that can be used for preparation of oral liquids (for example suspension or solution) (29). The committee also listed the desirable attributes of a paediatric dosage form namely:

1. Minimal administration frequency
2. Minimal impact on life style

3. Minimum, non□toxic excipients
4. Convenient, easy, reliable administration
   a. Palatable
   b. Requiring minimal manipulation by health professionals or carers prior to use (i.e. flexibility/adaptability of the medicine to account for developmental and size differences, with the ability to reliably divide the unit dose.)
5. Transportable and low bulk/weight
6. Easily produced, stable in a variety of climates
7. Affordable
8. Commercially viable

Source: WHO Report of the Informal Expert Meeting on Dosage Forms of Medicines for Children. Available from: http://www.who.int/selection_medicines/committees/expert/17/application/paediatric/Dosage_form_reportDEC2008.pdf2008

I am yet to see at least one such ideal paediatric dosage form which possesses all these desirable attributes.

Despite these recommendations by the high level technical bodies, the reality in ground level in many developing countries is still "paediatric unfriendly": situation in the public sector tends to be worse than that in the private sector. To name few issues: (i) paediatric oral formulations for many medicines are not included in the national essential medicine lists (30, 31), (ii) they are not prioritized in the national procurement and supply system (32), (iii) improper supply chain leads to poor access to end users (30, 32-37), (iv) equivalent dose of a medicine as a liquid preparation is more expensive than its tablet equivalent. At the time of publication of this reference in 2011, the price of 200 mg carbamazepine, an anti-epileptic medicine, as a liquid

formulation was about 40 times more expensive than the adult equivalent (38), (v) pharmaceutical industries and their agents are not interested in paediatric formulations as paediatric market is small with poor profit margin. For example only a small number of medicines are marketed in oro-dispersible formulations in Sri Lanka. Cost wise, oro-dispersible tablets, especially the brand products are not cheaper either.

Therefore, as an alternative to missing paediatric formulations, health care providers and parents are forced to resort to various methods to give medicines to small children such as crushing the tablets, dissolving tablets in solvents or opening and giving the powder contained inside the capsule. Consequently, these manipulated adult formulations are administered to children without any data regarding their bio-availability, efficacy and toxicity. In addition, the manipulation reduces the palatability particularly if the pill's format and matrix are designed to mask the bitter taste of active ingredients. A study from Tanzania reported that a large majority of parents/caregivers had experienced some problem with giving the manipulated adult dosage forms to their children and children either disliked the taste of or vomited them (39).

3. Different dosing regimens leading to dosing errors

"One size does not fit all"! (40). Paediatric dose should not be extrapolated from adult dose. They should be calculated based on weight, age or body surface area. Hence, weighing scales, calculators and paediatric formularies giving information on doses are crucial in prescribing and administering correct dose to children. The need to make dose calculations for each child at the bed side using above parameters increases the likelihood of medication errors, particularly dosing errors. Dosing errors of 10-fold or greater because of miscalculation or misplacement of the decimal point has been reported in the literature (41).

Getting medicine doses right for children also demands scored tablets, tablet cutters, computerization of dosing details, legible prescriptions, knowledgeable parents, competent prescribers and skillful pharmacists. Dosing error is not always over-dosing, but under-dosing is also prevalent which you will see in little while. Further, many medicines are available in large adult strengths in the market leading to inaccurate dosing when they are split or crushed for paediatric use. Currently the World Health Organization is spearheading a campaign for "make medicines child size" aimed at improving access to and use of safe and appropriate medicines for children globally.

4. Poor palatability and acceptability leading to refusal of medicines

Access has been identified by the World Health Organization as a major component to ensure right medicine in right formulation to every child. Access is having medicines continuously available and affordable at public or private health facilities or medicine outlets that are within one hour's walk from the homes of the population, and includes availability (physical access), affordability (economic access) and acceptability (socio cultural access) (42). Acceptability of medicines is more of a problem in children than adults. Taste of medicines plays a curial role in acceptability of medicines in children. As I stated earlier, crushing tablets and dissolving in various liquids reduces the taste especially when the matrix and format of the tablet had been included to mask the bitter taste of active ingredients. A recent pioneer randomized cross-over trial investigating the child and parent acceptability of and preference among four oral placebo formulations in infants and preschool children reported that the results do not support the historic approach that medicines should normally be given to young children as an oral liquid formulation as other formulations may result in equivalent acceptability (43).

In this first part of my lecture, I have managed to list the key differences in paediatric pharmacotherapy. Ignorance or lack of knowledge of these differences has led to various medicine-related tragedies in the past. Well-known example is that of in utero exposure to thalidomide, a benign medicine taken by mothers for vomiting leading to the birth of congenitally deformed infants (phocomelia) (44, 45) Those who forget the past are doomed to repeat it I have taken it upon myself to keep on reminding the healthcare providers and parents in Sri Lanka that medicines for children have its own independent range and horizon.

With this long line of reasoning to make my point that "children are not miniature adults" in terms of pharmacotherapy, let us look at some of our researches in paediatric pharmacotherapy.

The Oxford Dictionary defines research as "the systematic investigation into and study of materials and sources in order to establish facts and reach new conclusions". Medical research and academic medicine have their own range and horizon. Though the principles are the same, they differ from researchers in other disciplines in terms of justification, objectives, methodology, limitations and implications. When I was looking for a good definition for medical research and academic medicine, I came across the definitions given by the "Royal College of Physicians" which I am reproducing here (46)

> *"**Medical research** incorporates many types of study. Research carried out in science laboratories increases our knowledge about human physiology and disease. Clinical research with patients investigates what diseases look like in the body and how they develop, as well as exploring how new treatments and approaches might help. Population*

studies in the field of epidemiology explore disease trends and causes, looking to understand more about the public health measures that could help to improve these. Translational medical research refers to research undertaken to ensure new treatments and investigative knowledge actually reach the patients or populations for whom they are intended and are implemented correctly".

> *"**Academic medicine,** broadly defined is* the *discovery and development of basic principles, effective policies, and best practices that advance research and education in the medical sciences, ultimately to improve the health and wellbeing of individuals and populations"*

I have taken rational use of medicine, an important concept recommended by the World Health Organization as the foundation for the rest of my lecture.

Rational use of medicines:

In 1985, the World Health Organization defined the rational use of medicines as "patients receiving medications appropriate to their needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community" (47). A medicine is irrationally used if it is prescribed when there is little likelihood that it will have a beneficial effect or when the anticipated benefit is not worth the potential harm or the cost of the medicine. It occurs when the medicine prescribed is incorrect, inappropriate, excessive, unnecessary or inadequate.

Introduction:

Domperidone, an anti-emetic, is a commonly prescribed symptom reliever for children in Sri Lanka. However, domperidone is not in the WHO Model Essential Medicine List

for children: The reasons were that there was insufficient evidence to support the routine use of antiemetics for children with gastroenteritis, and potentially a high risk of adverse events, negating any significant benefit (48). In Sri Lanka, domperidone has been widely prescribed and used as an antiemetic in children without any concerns of its efficacy or adverse events. This led us to design a community based study to determine the prescribing practice of anti-emetics for children in Sri Lanka (49).

Methods:

Study design:

Cross sectional descriptive study

Study setting:

FourOsusala outlets of the State Pharmaceutical Corporation (SPC) which had pharmacists trained in medicine utilization data collection (Colombo 7, Nugegoda, Kurunegala and Kandy) and 4 private pharmacies paired for each Osusala Pharmacy where the pharmacists were willing to get the training (Colombo 4, Colombo 14, Kurunegala and Kegalle) were selected for the study.

Study population and inclusion criteria:

Allprescriptions containing at least one anti-emetic (domperidone, metoclopramide, promethazine, ondansetron and granisetron) dispensed for children under the age of 12 years during the study period.

Study period and duration:

Data were collected from all eight pharmacies for a period of four weeks in mid 2007

Data collection instrument:

A structured check list was designed to collect the following data from the prescriptions: (i) name of anti-emetic (ii) whether prescribed in generic or brand name (iii) brand name (iv) dosage form, dose, frequency and duration of anti-emetic treatment (v) quantity and cost of anti-emetic and (vi) names of co-medications.

Pre-testing data collection instrument:

This check-list was pre-tested and necessary changes were done prior to commencement of the main study.

Data collection:

Written prior permission was obtained from Authorities of SPC, branch managers of Osusala outlets and owners of private pharmacies included in the study. One pharmacist from each pharmacy was identified to collect the required data from prescriptions. All 8 pharmacists were trained by the investigators to collect data using the checklist. Most data could be collected from the prescription itself; however in some instances if the required data was not available in the prescription (e.g. indication) study pharmacists were instructed to get the information from the person who brought the prescription. Contact details of the investigators were given to the pharmacists if there is a query. Investigators also regularly contacted the study pharmacists to monitor the data collection procedures.

Data analysis:

At the end of the study period, the checklists were collected from the study pharmacists, and the data were classified, coded, entered on to the Statistical Package for Social Sciences (SPSS) and analysed according to the objectives.

Assessment of suitability of dosage forms for children:

This was done according to WHO recommendations(50). For example tablets were not considered suitable until 6 years of age.

Rationality of dose:

Recommended dose (mg/kg) was taken from product information leaflet and cross checked with British National Formulary. Therapeutic dose for a child was determined by using this information and approximate weight of a Sri Lankan child for the age. Overdose, under dose and impractical (cannot be measured) dose were decided by comparing the therapeutic and prescribed dose.

Off label use:

It was defined asuse of the anti-emetic in situations not covered by the product license or summaryof product characteristics i.e. at a different dose or frequency,in different clinical indications, in different age groups, administrationby an alternative route, or in a formulation not approved foruse inchildren.

Drug interaction:

Potential drug interactions between the anti-emetic and the co-medications were determined by referring British National Formulary and searching the literature.

Irrational prescriptions:

Based on the WHO'S definition of rational use of medicines, we considered the following as irrational prescriptions; (i) prescriptions with inappropriate indications, (ii) prescriptions with over or under dose for the age, (iii) prescriptions given for longer than the recommended duration,

(iv) prescriptions with unsuitable dosage forms for the age (v) prescriptions with co-medications which have potential drug interactions with the anti-emetic, and (vi) prescriptions which had co-medications contra-indicated for that age.

Ethical issues:

Prior permission was obtained from the authorities of the study settings to collect the data. Identity details of neither patients nor prescribers were collected. Identity of the study setting was kept confidential. Research proposal was submitted to the Ethics Review Committee of Faculty of Medicine, Colombo, and the investigators were informed that ethical approval is not required as the study amounts to an audit and participants are not identified.

Results

Description of study population:

One hundred and eighty five prescriptions containing at least one anti-emetic dispensed to children under the age of 12 years during the study period were included, 99 (53.5%) from the state pharmacy outlets and 86 (46.5%) from private pharmacies.

Type of anti-emetics: Domperidone was the most frequently (165 prescriptions, 89%) prescribed anti-emetic with very few prescriptions for promethazine (19 prescriptions, 10.5%) and metoclopramide (1 prescription, 0.5%).

Indication:

Anti-emetics were prescribed for the treatment of vomiting in 174 prescriptions (94%). In the remaining eleven prescriptions, promethazine (n=8) was given for allergic reactions and domperidone for sleep disturbances (n=1) and gastro-oesophageal reflux (n=2).

Age and gender:

Mean age was 4.48 years (SD = 3.03) with male to female ratio of 1.4:1. Almost half the prescriptions were given for children aged between 1 and 5 years with one fifth given for children under the age of one year.

Suitability of dosage form for the age:

Anti-emetics had been prescribed in different dosage forms, oral liquid dosage form in 54% of prescriptions followed by tablets (32.5%) and suppositories (11%). In 22 (12%) prescriptions, the dosage form was not suitable for the age.

Prescribed dose of anti-emetics:

Information on dose was not available for 8 prescriptions. Commonly prescribed doses were 5 mg (33.5%), 2.5 mg (24%) and 10 mg (23%) with a mean dose of 6 mg (SD = 5). However, when prescribed dose was compared with the recommended dose for the age of the child, 29.5% of prescriptions were found to be irrational (Table 1).

Frequency and duration of anti-emetic treatment:

Anti-emetics were mostly (62.2%) prescribed three times a day. In 17% of prescriptions they were given to be taken when required. Mean duration of treatment was 3.9 days (SD = 3.8) with a range of one day to one month. Anti-emetics had been given for two weeks or more in eight (4.3%) prescriptions.

Co-medications:

Anti-emetic was prescribed alone in 26 (14%) instances; 66 (36%) had one other co-medication, 44 (24%) had two and 49 (26%) had three or more. Oral rehydration salts (ORS) was prescribed only in 22 instances, less than anti-bacterial agents, paracetamol, antihistamines and bronchodilators.

Drug interactions:

Of the 159 prescriptions which contained another medicine in addition to anti-emetic, potential drug interaction with the prescribed anti-emetic was possible in 28 (17.6%). Most frequently observed potential drug interaction was domperidone and medicines which have anti-cholinergic properties (negate the action of domperidone) and domperidone and erythromycin (inhibits the metabolism of domperidone and increases the cardiac toxicity).

Off label use:

Seven prescriptions did not have the required information to assess whether they were off label use: Of the remainder, 52 (30%) prescriptions were off label. Further analysis showed that 71% of the off label use were seen in children under the age of 6 years (Table 1).

Irrational prescribing:

Eighty four (45.4%) prescriptions for anti-emetics in the study sample were irrational. There were 113 irrational uses in those 84 prescriptions as some prescriptions were irrational in more than one count. Of the 113 irrational uses 76% occurred in children under the age of 6 years (Table 2).

Children under the age of 6 years:

71% of off-label uses, 65% of inappropriate doses, 76% of irrational uses and 100% of unsuitable dosage forms were observed in prescriptions dispensed to children under the age of 6 years (Table 2).

Discussion:

Domperidone accounted for 89% of prescriptions confirming our hypothesis that it is the most frequently

prescribed anti-emetic for children in Sri Lanka. WHO model essential medicines list for children includes metoclopramide and not domperidone. However, In Sri Lanka, domperidone is included in the essential medicines list. Pharmacokinetically, too, domperidone would be preferred in children because it does not readily cross the blood brain barrier and is less likely to cause central side effects.

Secondly, only 12% of the prescriptions had unsuitable dosage form which was restricted to prescribing tablets in children under the age of 6 years. This may be justifiable in certain instances, given that tablets are cheaper than syrup, and a limited number of tablets can be bought instead of buying a whole bottle of syrup for a short course of illness.

Thirdly, about 30% of prescriptions had inappropriate doses. Domperidone dose ranges from 1.25 10 mg depending on age of the child. Syrup has 5 mg in 5 ml and tablet strength is 10 mg. Hence prescribers could easily give the correct dose.Some doses such as 7 mg and 3.8 mg were practically impossible to administer.The relatively higher prevalence of under-dose compared to overdose raises a question as to whether child really benefited from domperidone. Prescriber should be aware of the recommended dose and the strengths of commonly available domperidone. Sometimes calculating dose according to body weight leads to impracticalities requiring adjusting to the most approximate appropriate dose.

Fourthly, about 18% of prescriptions had co-medications which could have interacted with domperidone causing increased adverse effects or therapeutic failure. Domperidone should not be considered a no-risk alternative to cisapride, which has been withdrawn from the market, as domperidone is known to possess

electrophysiological properties similar to those of cisapride and class III anti-arrhythmic medicines (52).

Table 1: Distribution of key variables in the anti-emetics survey(49)

Variable	Indicators	Results
Duration	Mean	3.9 days (SD = 3.8)
	Range	1 day - 1 month
	> 2 weeks	4%
Dosage forms	Unsuitable for the age	22%
	Under dose	17%
	Over dose	6.5%
Dose	Impracital dose*	6%
	Irrational doses, Total	29.5 %
	Prescriptions with co-medications	159
Co-medications	Potential drug interactions	28 out of 159 (17.6%)
	Total	30%
Off label	0-5 years	21.3%
	> 5 years	8.7%
	Prescriptions	45.4%
Irrational use (Table 2)	Irrational uses *(some prescriptions were irrational in more than one criterion)*	113

** Doses like 1.8 mg which cannot be obtained from 5 mg / 5ml syrup or 10 mg tablets*

Table 2: Types of irrational prescriptions of anti-emetics for children in the community setting(49)

Reasons for irrational use	Frequency		
	0-5 years	> 5 years	Total
Inappropriate indication for anti-emetic	01	00	01
Over / under impractical does for the age	38	16	54
Longer than the recommended duration	05	03	08
Potential drug interactions	20	08	28
Unsuitable dosage froms for the age	22	00	22
Total irrational use	86 (76%)	27 (24%)	113 (100%)

Fifthly, prevalence of off label use in our study is about 30% as opposed to 10% of prescription given for children under primary care in the UK (53). In certain instances, off label use in children is unavoidable, but in our study majority of off label use could have been prevented if a little more attention had been paid.

Conclusion:

Domperidone was the most frequently dispensed anti-emetic for children in those districts, and there is no reason for other districts to be different. We have documented incorrect, inappropriate, excessive and inadequate use of domperidone in these prescriptions. Irrational use of domperidone was more prevalent in children under the age of 6 years than the older children.

We have used a very frequently prescribed medicine in children to demonstrate the extent and types of irrational use of

medicines in children. Healthcare providers and even parents may think that "domperidone is a harmless medicine, even if it is prescribed irrational, it does not matter". They are wrong in their assumptions on two counts.

1. Prescribers and mothers who used thalidomide also would have thought the same in late 1950s: Rest is history
2. There cannot be two standards of prescribing, one is for supposed to be "harmless medicines" and the other is for "harmful medicines": There are no "harmless medicines". It is the joined effort of all stake holders from manufacturers to patients that make a medicine safe.

Now, I will take another symptom reliever, paracetamol, to demonstrate the consequences of irrational prescribing and use of another supposed to be a "harmless medicine" in children.

Introduction:

Hepatotoxicity associated with acute paracetamol overdose was long recognised, but, the evidence at that time supported children, to be less susceptible to hepatotoxicity in acute paracetamol overdose due to differences in the hepatic metabolic pathway (54).Subsequently, evidence was emerging that paracetamol when used in high therapeutic doses for a prolonged period in children with viral fever could cause hepatotoxicity (55-63). This hypothesis led us to design a case control study to determine the cause-effect relationship between multiple supratherapeutic doses of paracetamol and hepatotoxicity in children with viral fever (64)

Methods:

Study settings and population:

The study was carried out at Lady Ridgeway Hospital for children (LRH) and Colombo South Teaching Hospital. Cases

and controls were from the children admitted to the paediatric medical wards to these two hospitals. Approval of the study was obtained from the institutional ethics committee.

Definition of cases:

Cases were children with fulminant hepatic failure: Fulminant hepatic failure was defined as acute liver disease complicated by hepatic encephalopathy occurring within eight weeks of the onset of the liver disease (65). Liver disease was defined as presence of fever, nausea and vomiting with increased alanine aminotransferase more than 3 times of the reference value.Diagnosis of fulminant hepatic failure was based on clinical and biochemical criteria. Fulminant hepatic failure was graded as follows, Grade I as minor disturbances of consciousness or motor function, Grade II drowsy, but responsive to commands, Grade III stuporous but responsive to pain, and Grade IV as unresponsive to pain (65).

Definition of controls:

Controls were children admitted with fever, and had an uneventful recovery without developing liver disease or any other complications. Up to two controls were selected for each case, matched according to centre, time of admission (within 2-7 days of admission of their matched cases), age and gender.

Exclusion criteria:

All cases in which the diagnosis of fulminant hepatic failure was questioned were excluded.All cases and controls whose parents could not be reliably interviewed were excluded. Investigations to rule out other possibilities as the cause of fever were carried out if the fever was persisting, and clinicians caring for these children chose the appropriate investigations depending on the clinical presentation.

Definition of exposure:

The recommended antipyretic dose of paracetamol for children is 15/mg/kg /dose and a maximum of 60mg/kg/day.A dose above 60mg/kg/day was considered as supratherapeutic.

Data collection:

A structured pre - tested questionnaire was used to obtain the following information from both cases and controls; demographic data, details of paracetamol intake, concurrent ingestion of other medications, presence of other risk factors for hepatic toxicity, clinical features, development of complications, results of laboratory investigations and outcome. The required information was obtained from interviewing the parents and doctors and from going through the case notes. Randomly selected six samples from both cases and controls were tested for common infective causes of fulminant hepatic failure in our region.

Lab investigations:

Paracetamol levels were estimated by fluorescence polarization immunoassay technology. The results of other laboratory investigations were obtained from the case notes.

Data analysis and Statistics:

Potentialfactors contributing to toxic effects of paracetamol on liver such as exposure to paracetamol, intake of supratherapeutic doses, average daily dose (mg/kg/day), duration of ingestion, total amount ingested during the current illness (mg/kg), and the type of paracetamol (adult or pediatric) were compared between cases and controls. Also, plasma paracetamol levels in the cases were compared with that of controls.

For further analysis, Grade II, III and IV hepatic encephalopathy were grouped together as severe form and Grade I as mild. Selected variables such as daily dose of paracetamol, duration of paracetamol intake and total dose of paracetamol ingested during the current illness were compared between mild and severe cases of hepatic encephalopathy. The data were analysed using Statistical Package of Social Sciences.Statistical methods used were chi-square and t test; p value < 0.05 was considered significant.

Results

I am presenting only a part of results which is relevant to this lecture. 25 cases and 33 controls were included in the study. Their mean age was 3.56 years (range 1 12 years)with male: female ratio of 1.4:1.

Exposure to paracetamol:

All 25 cases (100%)and 11 (33%) controls had consumed paracetamol during the current illness. Table 3 shows that all 25 cases gave a history of exposure to supratherapeutic dose (> 60 mg/kg/day) of paracetamol during each day of the illness compared to none in the controls. The mean daily paracetamol dose in cases was 145 mg/kg/day (SD = 57.8) compared to 40 mg/kg/day (SD = 8.3) for the control ($p < 0.001$). The mean duration of paracetamol intake prior to admission in cases was 3. 45 (SD = 1.3) days compared to 1.85 (SD = 1.2) days for the control group.

All cases received the adult paracetamol as opposed to 66% of the controls.The cases have ingested a mean total dose of 468. 36 mg/kg (SD = 206.52) paracetamol during the current illness. All (100%) cases and 19 (57.5%) controls showed presence of paracetamol in their plasma at the time of testing. Mean plasma

paracetamol level in the cases and controls were, respectively, 26.84 μg/dl (SD = 3.8) and 0.051 μg/dl (SD = 0.03) ($p < 0.001$).

Exposure to paracetamol in different grades of hepatic encephalopathy:

Table 4 shows thedose and duration of paracetamol ingestion in patients with mild hepatic encephalopathy compared to that of patients in severe grades. 83% (5/6) of the patients with severe hepatic encephalopathy gave a history of total paracetamol ingestion of more than 400 mg/kg over a period greater than three days during the current illness. On the other hand, 57.8% (11/19) of the patients with mild hepatic encephalopathy gave a history of total paracetamol ingestion of more than 400 mg/kg and of them only 31.5 % (6/19) had taken it for a period greater than 3 days. When the daily dose of paracetamol alone is considered, none with severe hepatic encephalopathy had ingested < 90 mg/kg/day.

Table 3: Average daily dose of paracetamol given to children with fulminant hepatic failure (N = 25) and to their matched controls (N = 33)

Daily does range (mg/kg/day)	Patients	
	Cases	Control
Not given	Nil	22
<60	Nil	11
60-90	02	Nil
91-120	10	Nil
121-150	05	Nil
151-180	05	Nil
181-250	03	Nil
>250	Nil	Nil
Total	**25**	**33**

Treatment and Outcome:

Seventeen (68%) cases were given N Acetylcysteine. Others were managed symptomatically.Three (12%) cases died and in two of them liver biopsy showed evidence of massive centrilobular necrosis compatible with paracetamol poisoning.

Table 4: Details of history of paracetamol ingestion in children with different grades of hepatic encephalopathy (N = 25; Grade 1= 19, Grade 2 & 3 = 6)

Exposure to paracetamol		Grades of hepatic encephalopathy	
		Grade 1	Grade 2 & 3
Daily does (mg/kg/day)	<60	Nil	Nil
	60-90	02	Nil
	91-120	07	03
	121-150	04	01
	151-180	03	02
	181-250	03	Nil
	>250	Nil	Nil
	Total	**19**	**06**
Duration (days)	Nil	Nil	Nil
	1-3	13	01
	>3	06	05
	Total	**19**	**06**
	<250	Nil	Nil
	250-400	08	01
	401-800	09	05
	>800	02	Nil
	Total	**19**	**06**

Discussion:

In this case control study, we have identified, daily dose of paracetamol (> 90 mg/kg/day), duration of exposure (> 3 days), total dose ingested during the illness (> 400 mg/kg) and exposure to adult paracetamol as the probable risk factors for hepatic toxicity in children with viral fever when they are exposed to multiple supratherapeutic doses of paracetamol.

Paracetamol was detected in the plasma of all cases and in 19 (57.5%) controls; the mean paracetamol level in cases was statistically greater than that of the controls. Although only 11 controls gave a history of exposure to paracetamol, 19 had paracetamol in their plasma. Paracetamol intake data, as in previous published reports relied on history alone (56,59,60). Hence it is possible that prescriptions given to controls also had "hidden" paracetamol. Since the majority of cases were mild (19/25) hepatic encephalopathy we could not determine statistically significant differences in the predisposing factors for severe form of encephalopathy.

If we carefully examine the definition of rational use of medicines, it says "in doses that meet their own individual requirements". This is the best example where irrational use in terms of "excessive dose" of a supposed to be "harmless" medicine leading to severe toxic effects.

Conclusion:

Our study despite some limitations provided evidence to support that exposure to supratherapeutic doses of paracetamol contributes to the development of fulminant hepatic failure in children with viral fever. Our findings revealed the risk associated with the use of an OTC medicine which is perceived as a safe and child friendly by doctors and parents.

Now the message is well known. In fact, I personally believe that people with hidden interests have exaggerated the issue to an extent that parents and doctors are sometimes resorting to alternative anti-pyretics. Hence, I want to stress the fact that the paracetamol still remains the anti-pyretic of choice for children. The risk of hepatic toxicity starts with doses very much higher than the recommended dose. In fact it is parents, prescribers and pharmacists driven hepatic toxicity. Educating the public with correct message and training the healthcare professionals to educate the patients are the need of the day.

Following this study, we made several recommendations to the policy makers, pharmaceutical industry, doctors and parents regarding cautious use of paracetamol for fever in children. It is interesting to note about 7 years later, in February 2013, the BNF has included therapeutic excess, defined as "the inadvertent ingestion of a potentially toxic dose of paracetamol during its clinical use" as a new category of paracetamol overdose (66).

Up to now, I was speaking about two symptom relievers: The following hospital based study focuses on anti-epileptic medicines, a major therapeutic group of medicine. The study also examines the dose, formulations, palatability and acceptability of medicines in children using anti-epileptic medicines as a model (67).

Introduction:

Effective treatment of epilepsy requires consistent plasma steady state concentration of the anti-epileptic medicine (AEM). This calls for rational selection of the AEM and an appropriate dosing regimen. Appropriate dosing regimen demands availability of AEM in strengths and formulations suitable for children (68). Unavailability of the suitable paediatric

formulation has to be overcome by one of two ways: Extemporaneous preparation (or compounding) of liquid formulations or manipulation of adult dosage-forms. Such manipulation could reduce the bioavailability as many AEMs are sparingly soluble in aqueous solutions and sensitive to effects that alter solubility or dissolution. Further, as I stated earlier, compliance and acceptability may be affected as the palatability of manipulated dosage-forms has not been studied.

This study was designed to determine the availability of AEMs in suitable paediatric formulations at the Lady Ridgeway Hospital (LRH) for Children, the methods of manipulation adapted by parents as an alternative for missing formulations and the palatability, acceptability and accuracy of dose of such manipulated dosage forms.

Methods:

A prospective cross sectional study was conducted at the OPD pharmacy of the LRH. Study population comprised children aged 12 and below with epilepsy who regularly attend the clinic and collect their AEMs from the OPD pharmacy. A consecutive sample of 109 children was recruited in one week in the latter part of 2008. Children attending the clinic for the first time were excluded.

The investigators visited the pharmacy, identified the children, explained the study to the parents, gave an information sheet and obtained consent. Data were collected from parents and older children using a pre-tested, structured, interviewer administered questionnaire, and analysed using descriptive statistics. Study protocol was approved by both Ethics Review Committees of the Faculty of Medicine, University of Colombo and LRH.

Results:

The mean age of study sample was 6.3 years (SD = 3.37), 15 children in 0-2 year, 38 in 2-6 year and 56 in 6 12 year age groups. They were on eight different AEMs with the majority(63%) on monotherapy. Sodium valproate (57%) was the most frequently prescribed AEM followed by carbamazepine (16%). None of the prescribed AEMs were available in suitable paediatric formulations. Except a 2 year old for whom parents were buying sodium valproate syrup from private pharmacies, the others, irrespective of their ages, received adult strength AEM tablets. Parents were instructed by pharmacists to segment the un-scored adult tablet. Of the 53 children under the age of 6years, parents segmented the adult tablet: in 45% into half, in 7% into quarter, in 6% into three-quarter and in 3% into one-eighth.

Parents used diverse methods to encourage children swallow the whole or segmented tablet. Majority in 2-6 (60.5%) and 6 -12 year (78.5%) age groups managed to swallow the tablet whole/part. A small minority (13.3%) of children in 0-2 year age group chewed the AEM with the rest receiving it crushed and mixed with a variety of vehicles including water (54.5%), breast milk (17%), honey, sugar, co-prescribed syrup and food.

On assessing the palatability of these medicines in the 5-12 year age group using a Likert scale majority graded valproate (65%) and carbamazepine (64%) as of average taste. About one-fifth of parents always encountered problems in administering valproate with half finding it hard to crush; when broken, the remaining half often disappears (melts) or children refuse to take them claiming it was very bitter. This led the parent to purchase more tablets out of pockets.

Table 5: Methods used by parents to make their children swallow the AEDs (67)

Methods	0-2yrs	2-6yrs	6-12yrs	Total
Swallows whole/part of the table with water	0	23	44	67
Swallows broken/crushed tablet mixed with various vehicles	13	14	8	35
Swallows chewed tablet (whole/part) with water	2	1	4	7
Total	15	38	56	109

Discussion:

Despite the regulatory authorisation of paediatric formulations of AEMs and inclusion of liquid formulations of carbamazepine and sodium valproate in the National List of Essential Medicines, young children received manipulated adult dosage forms. Though the study reports one week data, the pharmacists at LRH reported that they rarely had liquid formulations of AEDs.

Tablet splitting of AEMs by parents on the instructions of pharmacist to overcome stockouts seems to be a common practice. The practice of segmenting tablets assumes there is uniform distribution of the active medicine within the tablet and the ability to segment the tablet accurately. Researchers have determined the level of weight uniformity of segments from tablets cut into halves by pharmacists. They collected 560 such split tablet halves, determined their weights using the USP criteria, and concluded that tablet splitting resulted in an unacceptably high incidence of weight variation (69).The act of

crushing tablets which are not designed to be administered in this way and using untested vehicles alter the pharmacokinetics of medicines (70).This could be significant for medicines withnarrow therapeutic range such as AEMs.

Conclusion:

Even at the Premier Children Hospital, key essential medicines such as AEMs were not available for children in suitable size and formulation. Young epileptic children were receiving manipulated adult dosages, often in inaccurate doses with unproven bioavailability and questionable palatability. We have long way to go before we can ensure "the right medicine in right formulation to every child".

Let us recall what I said about irrational use of medicines: "A medicine is irrationally used if it is prescribed when there is little likelihood that it will have a beneficial effect or when the anticipated benefit is not worth the potential harm or the cost of the medicine" Let me tell you a case report where the "anticipated benefit was not worth the potential harm of the medicine" Though, the patient concerned is not a child, I intentionally selected this example to demonstrate the importance of riskbenefit assessment in every day practice. With wide general practice seen in our country, children are not immune to similar issues.

Nicolau syndrome

(livedoid dermatitis), a known but rare adverse reaction at the site of intramuscular medicine injection was first described in 1920s following the injection of bismuth. Subsequently it has been reported with intramuscular administration of medicines such as non-steroidal anti-inflammatory medicines (NSAIDs), local anaesthetics, corticosteroids, antibiotics, interferon alpha

and sedatives (71-76). Nicolau syndrome presents with acute severe pain and localized erythema during intramuscular injection İeading shortly to cutaneous, subcutaneous (necrotizing fasciitis) and muscular necrosis (71-75). Complications include respiratory distress syndrome, renal failure, shock, and disseminated intravascular coagulation (73).

In 1998, three fatal cases of Nicolau syndrome following the intramuscular injection of diclofenac to the deltoid or anterolateral aspect of thigh were reported to the national ADR centre. Review of the literature and product information leaflets showed that diclofenac should be administered deep only to the upper and outer quadrant of the buttock. This led the DrugEvaluation Sub Committee to recommend the following with regard to the future use of intramuscular diclofenac (i) giving only by deep intramuscular injection into the upper outer quadrant of a buttock, (ii) considering risk- benefit before prescribing, and (iii) using alternative routes such as suppositories.

Eight years later in December 2006 a similar fatal case was reported from the National Hospital of Sri Lanka (NHSL). However, the site of injection was the upper outer quadrant of the buttock in keeping with the recommendations. A 23- year old man received an intramuscular injection of diclofenac from his general practitioner for fever and arthralgia associated with chickungunya. The following day he was admitted to NHSL with symptoms suggestive of necrotizing fasciitis. In spite of intensive surgical and medicine treatment he died on the following day. Post-mortem showed that the cause of death was septicaemia following necrotizing fasciitis (77).

In this instance, there was nothing irrational in the selection of medicine, dose, route and site of administration. But the risk-benefit analysis was irrational. The anticipated benefit of pain relief was not worth for the potential harm which could lead to death. Yes, arthralgia in chickungunya is severe and sometimes disabling, but whatever its severity, it does not demand a therapy which has the potential to kill a young, healthy adult. My message again and again to prescribers and other healthcare professionals is "there are no safe medicines there are only safe healthcare professionals".

Let me conclude my presentation with some final notes:

1. Children are not miniature adults: Let us remember this whenever we treat children
2. Paediatric clinical pharmacology is a fast growing discipline: Let us keep up the pace
3. Many instances of irrational use of medicines are easily preventable: Let us start from today
4. There are no "harmless" medicines in the pharmacopoeia: Let us be the protectors
5. Children has poor access to right medicines in right formulations: Let us change it

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7. Elective committee, Faculty of Medicine, University of Colombo

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