Quality use of medicines: The vomiting child

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The challenge of rational medicines use in children is compounded by the presence in the clinical relationship of the parent – often anxious, concerned about the welfare of the child, facing many competing demands (such as a need to avoid spending many hours away from work) and thus frequently demanding of medicines that will deliver quick symptomatic relief. This should be a familiar scenario for any family physician that has treated a child with acute gastroenteritis, with associated vomiting. While demands for anti-diarrhoeal agents, such as loperamide, are perhaps easier to deflect, demands for something that will stop the vomiting are less easily handled. If the WHO P-drug process is to be applied, the first step is to be clear about the problem. Acute gastroenteritis (AGE) is defined as "diarrheal disease of rapid onset, with or without accompanying symptoms and signs, such as nausea, vomiting, fever, or abdominal pain".[1] This is probably the most common cause of vomiting in children that is encountered in family practice. Clearly, a quite different analysis is needed for other causes of vomiting. As the question here is the management of the vomiting component, the therapeutic objective has to be carefully constructed. Older children and parents will clearly motivate for the need for symptomatic relief. However, many clinicians would argue that stopping the vomiting is important to avoid dehydration and to aid the administration of fluids and food. Most will, nonetheless, acknowledge that the vomiting is self-limiting – as the American Academy of Pediatrics (AAP) puts it: "as dehydration and electrolyte imbalance are corrected by the repeated administration of small amounts of the [oral rehydration] solution, vomiting often decreases in frequency. As the vomiting lessens, larger amounts of the solution can be given at longer intervals".[1] *(SA Fam Pract 2003;45(4):20-22)*

BACKGROUND TO LITERATURE

Early papers on this subject seemed so clear – it was pointed out that emetogenesis was associated with two distinct neural sites. The emesis centre was the site of action for anatomic disorders, and was amenable to intervention with antihistamines, while the chemoreceptor trigger zone was associated with vomiting caused by toxic and metabolic problems, and was blocked by phenothiazines and related compounds. Wyman and Wick concluded confidently "a pharmacological approach to this problem can be logically constructed".[2] Common agents prescribed in this patient population have therefore included promethazine and cyclizine (antihistamines), prochlorperazine (a phenothizazine), and metoclopramide and domperidone (dopamine antagonists). More recent additions have included the $5HT_3$ antagonists, such as ondansetron.

Attempts to create evidence-based guidelines for gastroenteritis management have all seemed to skirt the issue of vomiting, usually with a statement along these lines: "Consensus opinion is that antiemetic drugs are not needed".[1] A 2001 UK guideline noted that "the level of published evidence on which recommendations are based is poor".[3] While it made a firm statement that "antidiarrhoeal and antimotility agents are not clinically beneficial, ... and their side effect profile is unacceptable", citing firm Level I evidence (from "at least one systematic review of multiple, well designed randomised controlled trials"), it said little if anything about the use of antiemetics. An updated guideline from the Cincinnati Children's Hospital could go no further than to state "antiemetics are not recommended in children with AGE", citing only review articles and consensus opinions.[4] The AAP practice parameter is also the only reference cited in a very extensive review of the problem, from the family practice perspective, published in 1999.[5]

The family practitioner attempting to apply the P-drug process therefore faces considerable challenges in finding appropriate evidence of efficacy and safety, before even getting to considerations of suitability and cost. Those articles that can be sourced, for example from a MEDLINE search, are often in obscure or old journals.

Reliance on abstracts for information is risky, but at times unavoidable.

EVIDENCE FOR EFFICACY AND SAFETY

Efficacy

Evidence for the efficacy of the older agents is not easily obtained.

The challenge of measuring efficacy in a self-limiting condition is well illustrated by recent papers on the use of ondansetron. The $5HT_3$ antagonists are generally used in more severe settings (e.g. peri-operatively and for chemotherapy-associated nausea and vomiting), but have been suggested as less toxic alternatives in children with AGE.[6,7]

Ramsook *et al* randomised children aged 6 months to 12 years who had vomited at least 5 times in the preceding 24 hours to receive either oral ondansetron (n=74) or a taste- and colour-matched placebo (n=71), in addition to standard oral rehydration. During the observation period in the hospital emergency department, the median number of episodes of vomiting was 0 in both groups, ranging from 0-7 in the placebo group and 0-2 in the ondansetron group. Based on patient diaries and follow-up telephone calls, the median number of episodes of vomiting in the 48 hours after discharge from the emergency department was also 0 in both groups, even though 5 additional doses were administered every 8 hours at home. Response to the study has been critical, and has pointed out that the study was underpowered to show a difference, if one exists, as the failure rate with oral rehydration therapy (ORT) is as low as 5%. Of added concern was the observation that those treated with ondansetron had a marked increase in the number of stools in the first 24 hours (mean 4.70) compared to those treated with placebo (mean 1.37).

Reeves *et al* considered patients in a wider age band (1 month to 22 years), and with, perhaps, more severe disease, as all required intravenous fluid replacement. This might well have reflected local practice more than severity, as the number of episodes of vomiting in the previous 24 hours ranged widely, from 3-30 in the ondansetron group (n=54) and from 3-40 in the placebo group (n=53). Three prior episodes was the minimum for inclusion. The median number of episodes was not statistically different, being 7 and 8 in the ondansetron and placebo groups respectively. Complete cessation of vomiting was seen in 38 (70%) of those given a single dose of intravenous ondansetron and 27 (51%) of those given the placebo. *A priori* conditions for admission included prior use of intravenous hydration for the same illness or a serum carbon dioxide ≤14mEq/l. A sub-group analysis of those with presentation serum carbon dioxide ≥15mEq/l and who had not previously been seen for intravenous hydration was used to determine whether the use of ondansetron reduced the need for admission. Of those in the sub-group given ondansetron, only 3/47 (7.5%) were admitted, compared to 11/43 (23%) in the placebo group (p=0.04). Their conclusion was therefore that "adding ondansetron to standard intravenous rehydration therapy significantly decreased the amount of vomiting in children with gastroenteritis", and that "in first-time treated children, with a serum CO_2 ≥15mEq/l, ondansetron significantly decreased the hospital admission rate".

However, in their paper, they did acknowledge that hospital admission rates vary considerably, and that their results would not be easily generalisable. They also admitted that "some patients may have recovered with aggressive oral rehydration therapy without the use of other therapy". Finally, the cost involved must be balanced against the fact that their results show that, even in the non-acidotic sub-group, the number needed to be treated to avoid 1 admission would be 4. The small numbers involved, however, could only be stated (with 95% confidence) to fall between 2 and 11. Similarly, the number needed to treat (NNT) to prevent any vomiting at all would be 5 (95%CI 3-77).

Safety

Evidence for the unacceptable side effect profile of the antiemetics comes predominantly from case reports. Acute dystonic reactions have been noted with the use in children of promethazine, prochlorperazine, domperidone and metoclopramide.[8,9,10] Symptoms of neck stiffness have been mistaken for meningism.[11] A Saudi case series included 24 children seen with acute dystonic effects after being given metoclopramide – in 19/24 cases the reason for prescribing the drug was listed as vomiting.[12] The authors noted that, despite questions about the value of metoclopramide in its classical paediatric indications, "it remains a popular antiemetic, used widely in developing countries as it is readily accessible to patients and prescribers". An Australian review of the management of acute dystonic reactions noted that most were related to either antiemetic or antipsychotic use, calling them a "common and distressing complication".[13] Campbell pointed out that the best predictor of such an event was a previous history of having had one – noting also that "antiemetics are usually avoided in children, and need not be given for short-term problems such as gastroenteritis". While problems have been noted with cyclizine when ingested by children in moderate overdose (average 200mg, equivalent to 4 tablets),[14] an additional drawback was noted in the US where teenagers were found to be abusing the agent for its hallucinogenic effects.[15]

The net result of the literature review of efficacy and safety seems to indicate that antiemetics should not be used, making consideration of suitability and cost issues unnecessary.

QUALITY USE OF MEDICINE IN PRACTICE

One last issue deserves attention. There is still evidence of considerable resistance to the message that antiemetic use is not necessary, and associated with an unfavourable benefit to risk ratio. A recent survey of 593 specialist clinicians in the US showed that 60.9% had used an antiemetic for paediatric gastroenteritis at least once in the previous year.[16] The most common reason advanced was to prevent further dehydration, and the most common concern was the potential for side effects

(reported most frequently with prochlorperazine). Per rectum promethazine was the most commonly used option. It has been shown that awareness of the AAP guidelines on ORT is associated with greater use of that intervention.[17] Many years before the issue of the AAP guidelines, it was shown that while specialist paediatricians were more likely to suggest clear fluids in children with vomiting than practitioners without specialist training, the opposite was true for the use of drug treatments.[18] Old ideas take a long time to exit the profession, and new ideas that propose that a less expensive, even homemade, intervention is more effective than the results of complicated technology are counterintuitive.

Personal experience is also a problem – after a 1994 paper on ORT in Australian Prescriber, a general practitioner wrote that he found specialist advice on the issue of little practical use – instead he suggested telling the mother "nothing by mouth for 3 hours and then try a little water – if rejected, wait another 3 hours and try again, but ring me at any stage if you are getting anxious".[19] He contended that mothers, anxious because of media attention on the need for aggressive ORT, "every time the child vomits, they feed 30ml or so of ORS which the irritated stomach – not realising the good intention – promptly returns, usually with interest". The dangers of that approach should be obvious.

In an editorial accompanying Burkhart's 1999 review, Avery noted that the "how" was as important as the "what" – that success in developing countries might be due to the fact that "ORT is administered by giving a teaspoon of solution every few minutes over a period of hours", whereas failure in the US was perhaps because "thirsty and hungry infants who are given a bottle are likely to consume too much too fast, with swallowed air, and then will promptly vomit".[20] Busy parents (and emergency department staff) are more likely to prefer a quick intravenous solution, or a drug. Is family practice that different?

CONCLUSION

After 30 years, what evidence we have says – drugs are unnecessary, clear fluids are inappro-priate (either too low in sodium, as with colas, commercial sports drinks and teas, or too high, as in chicken broth) - ORT is the only quality option.❐

Please refer to the CPD questionnaire on page 53.

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