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Harm to a child caused by the off-label use of prochlorperazine maleate tablets due to the discontinuation of licensed prochlorperazine mesilate liquid in the UK

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ABSTRACT

Prochlorperazine is a commonly used medicine to treat nausea and vomiting. The only liquid formulation in the UK was discontinued in November 2022 due to safety concerns. One alternative option available is to use crushed tablets instead. Crushing and mixing tablets in water to produce a liquid is a widespread practice in paediatrics. However, there is often little evidence to support this practice.

In this case report, a patient established on liquid prochlorperazine mesilate who was switched to crushed prochlorperazine maleate tablets experienced significant harm. The child's vomiting became uncontrolled and led to multiple healthcare attendances and a prolonged hospital admission. Control was re-established by increasing the prochlorperazine dose to accommodate for loss of drug during preparation. Care should be taken when converting prochlorperazine mesilate liquid doses to crushed prochlorperazine maleate tablets, and the doses used should not be treated as equivalent.

BACKGROUND

It is widely acknowledged that the administration of many medicines to children is outside of an established evidence base.[1 2] This creates an environment where medicines may be used in ways that expose patients to potential safety events—for example, the use of unlicensed medicines or the off-label use of a licensed medicine. Both these scenarios have been shown to increase the risk of moderate harm when compared with medicines that are used within their marketing authorisation.[3]

In the case of enteral administration, choosing the right medicine and administration method for a child is complex and challenging for both healthcare professionals and families. Individual characteristics that may affect these choices include the age, diagnosis, route of administration (eg, oral or enteral feeding tube) and tablet swallowing ability. Each characteristic has the potential to increase the likelihood that a medicine will need to be used off-label or that an unlicensed medicine is required.

The treatment of refractory vomiting for children with brain cancers demonstrates many of these issues. Pharmacological treatment is necessitated by the physical damage to the brain caused by surgery and radiotherapy. In addition, ongoing chemotherapy adds further complexity. It is an area with little research to guide practice. The medicines used and evidence to guide their use are extrapolated from studies on either chemotherapy-induced nausea and vomiting[4] or postoperative nausea and vomiting.[5]

Prochlorperazine is one of many antiemetics available to treat children with nausea and vomiting. It works in the brain primarily by blocking dopamine receptors, but also weakly antagonises adrenergic, histamine, serotonin and muscarinic neurotransmitter pathways.[6] This makes it a useful treatment option for children with brain tumours because it blocks multiple pathways. Another useful characteristic of prochlorperazine is that it was available as a liquid, tablet, buccal tablet and injection. This gave flexibility about administration and many possible options from which families could choose.

In the UK in November 2022 the Medicines and Healthcare products Regulatory Agency (MHRA) issued a product recall of prochlorperazine mesilate liquid after N-nitrosomethylphenylamine was detected above the recommended safe limit in this formulation.[7] The only licensed liquid formulation of prochlorperazine was subsequently removed from the market by the manufacturer. Therefore, families and healthcare professionals have been forced to find alternative treatments.

An alternative option is to crush the licensed tablets and mix with water to create an extemporaneously prepared liquid at the point of administration. While this may have some advantages such as availability and cost, it also exposes the patient to the risks previously mentioned that are associated with using a licensed product off-label.[3] In this example, harm may be caused by under-dosing. This is because prochlorperazine is used as two different salts depending on the formulation. Prescribing information for prochlorperazine is usually expressed only as the base drug because there is no conversion needed between salts. However, there are important physiochemical differences between the two salts.

In the liquid, prochlorperazine mesilate is used which has an aqueous solubility of 2 g/mL.[6] However, prochlorperazine maleate is used to formulate tablets which only has an aqueous solubility of 15 mg/L.[8] Therefore, it is unlikely that a sufficient amount of water could be practically measured and administered to sufficiently dissolve the prochlorperazine maleate contained within a single tablet.

The aim of this case report is to highlight this risk and discuss the implications in the context of a child with complex health needs.

CASE PRESENTATION

A boy in early childhood (weight 20 kg) was diagnosed with a malignant brain tumour called a medulloblastoma. The child had surgery in February 2022 to remove the tumour, followed immediately by radiotherapy over the following 2 months. Following surgery and radiotherapy, the patient experienced refractory vomiting that required medical management.

He was established on a treatment plan of regular ondansetron (4 mg/5 mL liquid, Advanz Pharma) 4 mg three times a day and prochlorperazine mesilate (5 mg/5 mL liquid, Aventis Pharma) 5 mg three times a day. All medicines were given using a nasogastric tube due to an aversion to oral medication as a result of psychological trauma associated with his previous treatment. A nasogastric feed was also recommended by his dietician to ensure his nutritional needs were met. His parents were trained on how to use the nasogastric tube for administering feeds and medicines in accordance with hospital guidance and procedures.

The patient started the chemotherapy according to the International Society of Paediatric Oncology Primitive Neuro-Ectodermal Tumour Medulloblastoma (SIOP PNET 5 Medulloblastoma) protocol[9] consisting of four cycles of treatment in April 2022. Each cycle consisted of intravenous cyclophosphamide (1000 mg/m^2 on days 1–2) and vincristine (1.5 mg/m^2 on day 1), followed by a 3-week break. Intravenous cisplatin (70 mg/m^2 on day 1), intravenous vincristine (1.5 mg/m^2 on days 1, 8 and 15) and enteral lomustine (75 mg/m^2 on day 1) were then given, followed by another 6-week break. This was then repeated four times to complete the three cycles of chemotherapy treatment (see figure 1).

The first two cycles were tolerated relatively well. The patient's vomiting was controlled before, during and after chemotherapy when his antiemetics were escalated and de-escalated according to national chemotherapy-induced nausea and vomiting guidelines.[4] His weight was maintained, he was eating small amounts of solid food by mouth, and he was attending school in between hospital appointments.

In mid-October the family were informed that prochlorperazine mesilate liquid would not be available to them anymore. The hospital was unable to find another liquid formulation and therefore the family were told that licensed prochlorperazine maleate 5 mg tablets could be used instead in an off-label way. The family were instructed to continue the same dose of 5 mg three times a day by crushing a 5 mg tablet and mixing with some water, then to immediately administer this suspension down his nasogastric tube.

Within a few days of changing from liquid to crushed tablets the family reported an increase in vomiting symptoms. They were struggling to administer his nasogastric nutrition and the frequent vomiting was disrupting daily life. There was also a noticeable change in the patient's behaviour and the child stopped attending school.

The family first presented to their local hospital assessment unit on two separate occasions at the start of November (see figure 1). Each time the patient was assessed, given intravenous ondansetron and a fluid challenge. Following cessation of vomiting they were sent home with instructions to restart his feeds and medicines. However, the vomiting returned as soon as nasogastric feeds and medicines were restarted at home.

Figure 1 Timeline of events.

Finally, after the third cycle of chemotherapy in mid-November and after persevering for almost a month at home, the family presented to the specialist oncology unit at the children's hospital. They were admitted for intravenous fluids, intravenous antiemetics and further assessment.

On day 1 of admission the vomiting was severe enough that all nutrition and medicines by nasogastric tube was stopped. The antiemetics on admission were changed to intravenous ondansetron 4 mg three times a day and intravenous levomepromazine 0.5 mg twice a day. Intravenous crystalloid fluids were prescribed for hydration. The patient was very withdrawn from his surroundings and bed bound for most of the day.

By day 3 the vomiting had subsided enough that nasogastric feed was restarted and the antiemetics were also changed back to nasogastric. Levomepromazine was converted to levomepromazine 1 mg twice daily (using crushed tablets) and ondansetron was converted to 4 mg three times a day using liquid as before. Erythromycin was also started to see if that would help with gastric emptying.

INVESTIGATIONS

The initial investigations were led by the medical team. They could not find a medical explanation for the worsening control of vomiting after clinical examination and biochemistry tests. Biochemistry tests included a full blood count, urea and electrolytes, and liver function tests.

TREATMENT

On day 6 of the hospital admission the family had failed to make much progress and experienced a further deterioration in the control of the child's vomiting. This prompted a medicines review which was conducted by a specialist children's oncology pharmacist who reviewed the entire history with the family. The possibility of dose equivalence between liquid and tablet form of prochlorperazine was discussed. While intravenous levomepromazine was effective, it was also very sedating and it was not possible to continue this outside hospital.

The pharmacist checked with the family that there were no issues with administering medicines via the nasogastric tube and the dose was flushed with water before and after each dose. There was not felt to be any interactions with the feed as this had remained unchanged throughout his chemotherapy treatment.

The family confirmed that they were crushing the tablet using a tablet crusher and then adding water to produce a suspension. The family reported that, despite their best efforts, some crushed tablet remained undissolved and adhered to the surfaces of the tablet crusher. The pharmacist then simulated the administration of prochlorperazine by attempting to dissolve a tablet in water and confirmed that the tablets do not dissolve despite repeated agitation and time. Therefore, it was agreed that there could be significant loss of the dose each time it was prepared and administered.

In agreement with the family, the prochlorperazine was restarted at an increased dose of 7.5 mg using crushed tablets via the nasogastric route three times a day. The increased dose was based on previous studies showing that up to 50% of dose may be lost when preparing a medicine in such a manner.[10 11] It was also pragmatic as it meant the dose would be one and a half tablets.

This new dose was overlapped with 24 hours of intravenous levomepromazine to help reduce the vomiting sufficiently to allow for the absorption of the nasogastric prochlorperazine. A quarter of a hyoscine patch changed every 3 days was also started to give an antimuscarinic effect in case motion sickness was contributing to the vomiting.

The family had previously researched using homeopathy but were advised against this from the clinical team due the lack of safety data when used alongside chemotherapy. Acupuncture was also considered but the patient was unable to tolerate this due to a phobia of needles. The family were very conscious of avoiding smells (eg, from cooking, cleaning products or scented candles) and used relaxation techniques (eg, massages and baths).

OUTCOME AND FOLLOW-UP

On day 7, after 24 hours of increased dose prochlorperazine, the vomiting had subsided enough that intravenous levomepromazine was stopped and nasogastric feeds restarted. Intravenous ondansetron was also converted back to the enteral route at the same pre-admission dose. On day 8 erythromycin was stopped due to faecal incontinence, but the hyoscine patch was continued as there were no perceived antimuscarinic side effects. By day 10 the patient was fully established on the pre-admission nasogastric feeding plan. The patient appeared much happier, was moving around the ward and visiting the playroom. The family were discharged back to their home.

The patient was followed up in the routine oncology clinic 2 weeks after discharge from hospital. The family reported that they had regained some form of normality which had not been experienced since the liquid was changed to tablets over a month previously. Figure 1 shows a timeline to illustrate the case, the temporal nature of the adverse events surrounding the change in formulation, and the resolution of unplanned attendance at healthcare institutions. Further follow-up included an end of treatment assessment in January 2023 which also found no evidence of toxicity or adverse effects from this increased dose.

DISCUSSION

Numerous studies have shown that crushing and mixing tablets in water to administer a dose which is a proportion of a tablet will result in under-dosing.[1] For example, studies investigating the crushing and mixing with water of aspirin tablets to produce a suspension have shown significant amounts of variation in dose uniformity.[10 11] This is especially true of non-dispersible aspirin tablets, which have been shown to give less than half the intended dose.[10] This is thought to be due to the poor solubility of aspirin, which may be representative of most drugs given via the oral route, causing a degree of sedimentation and lack of uniform dispersion of drug throughout the liquid.

The administration of medicines down a nasogastric tube also presents further risks for variability in the dose administered due to physical interactions. There are many circumstances for such interactions to occur, but some specific examples include the adsorption of drug to enteral tube surfaces[12] and the binding of drug to proteins in feeds.[13] Some of these may have been influencing this case, but the major factor will have been the poor solubility of prochlorperazine maleate and the failure to make a uniform suspension prior to administration using the nasogastric tube.

Despite this evidence, it is still common practice to use medicines in this way both in the UK and also across the EU.[14] The lack of age-appropriate formulations (ie, liquid formulations for young children) together with individual circumstances (eg, feeding tubes, palatability, ability to swallow tablets, lack of therapeutic drug monitoring) create the conditions whereby tablets are used in this manner. Furthermore, the common reference sources for dosing in children (eg, British National Formulary for Children) can be ambiguous about what the method of administration is for a particular dose. Unfortunately, there is very little published information about the effectiveness of specific formulations and preparation methods.

In certain specialist areas such as neurology, switching between formulations is undertaken with careful consideration and management of the risks involved. For example, the MHRA

Learning points

- ⇒ The administration of medicines via the enteral route to children continues to be an area of pharmacy practice which is poorly understood.
- ⇒ Healthcare professionals should consider the risk to patient safety with changing any formulation or method of enteral administration for any patient who is already established on a treatment.
- ⇒ Healthcare professionals should work together with families when availability problems occur to identify specific risks for the individual circumstances and how effectiveness will be monitored.
- ⇒ If a patient's clinical condition deteriorates after a substitution, consider the role that changes to dose, formulation or method of administration may have had.
- ⇒ In this specific example of substituting prochlorperazine maleate crushed tablets for prochlorperazine mesilate liquid, the poor solubility of prochlorperazine maleate presents a risk of underdosing that may lead to reduced efficacy of treatment.

Parents' perspective

As a parent, watching your child fight cancer is unimaginable, forced to wear multiple 'hats', parent, carer, advocate … for our child. Vomiting was a persistent challenge and the relief of achieving a regime that was effective allowed our child to regain some form of normality. This included attending school between treatments.

When the liquid prochlorperazine was replaced with tablets, everything changed and vomiting became uncontrolled. We entered a vicious cycle whereby medication was unable to be absorbed and feeds were not tolerated. The result was significant weight loss, reduction in energy, and reduction in quality of life for our child and overall as a family. The frequent trips to hospital meant disruption to my partner's ability to work and also the care of our newborn baby.

As parents we faced a perception of disbelief from the medical professionals, given our child was able to successfully undertake fluid challenges while on IV antiemetics. By this point in treatment we were acutely aware that IV antiemetics masked the vomiting and prompted discharge, swiftly followed by reoccurring vomiting as nasogastric antiemetics were reinstated. At no point did any healthcare professional appear to consider the change in medication to tablets as the primary source of the problem. We even began to consider if this was a sign that our child's brain cancer had come back.

In November we were again faced with a water challenge and plan for discharge; with concern for our child's welfare we refused discharge. To make matters worse, we were told that it could be parental anxiety over our child that was a contributing factor to vomiting.

We welcomed the review of our child's medication by the clinical pharmacist and were willing to trial any new combinations. The increased doses to compensate the loss by crushing the tablets has made a significant impact. Nasogastric feeds are tolerated and increased with a positive impact to weight and energy levels. Our child has returned to school and has been able to participate in more social activities. Vomiting has remained minimal and controlled.

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has produced guidance that helps professionals to consider the risks involved with switching formulations of antiepileptic drugs (AEDs).[15] The conversion of AEDs is also supported by the use of therapeutic drug monitoring which provides clinicians and families with a safety net regarding dose equivalence. The underlying principle of this guidance—that AEDs have narrow therapeutic windows with potentially serious consequences of therapeutic failure—may be relevant to other therapeutic areas in specific circumstances.

Another factor adding to the complexity in this area is the lack of suitable alternatives. With regard to dopamine antagonists, various other options are not available due to a lack of availability of UK licensed medicines (eg, metopimazine), restrictions on use by regulators (eg, metoclopramide) or lack of approval from local formularies (eg, antipsychotics such as olanzapine). Initiatives to support children to take tablets to avoid liquid formulations altogether are developing,[16] but may not be appropriate for all families.

This case highlights the complexity of pharmacological treatment of refractory vomiting for children with brain tumours. It is a constantly changing environment and treatment requires close working relationships between families and professionals to provide careful and constant monitoring of treatment.

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