Loperamide toxicity in severe protracted diarrhoea

Sir,

We read with interest the paper by Sandhu et al. on loperamide in severe protracted diarrhoea1 paying particular attention to the doses they used. In an earlier paper2 they reported using doses of loperamide of up to 4 mg/kg with impressive results, and in this one, although 5 out of the 6 children described received less than 1 mg/kg/day, I was treated with 3·8 mg/kg/day. We should like to report the case of an infant age 4 months with severe diarrhoea caused by a short bowel syndrome who exhibited signs of central nervous system toxicity when treated with such a dose of loperamide. We believe this to be the only account of such toxic effects following a course of loperamide in this therapeutic range.

This infant had necrotising enterocolitis in the neonatal period necessitating resection of the greater part of his ileum. An anastomosis between the proximal and terminal small intestine left 38 cm of small bowel measured from duodeno-jejunal junction to ileocaecal valve. Loperamide was prescribed first at 6 weeks of age at a dose of 6 mg/day increasing to 18 mg/day over the next 10 weeks. It had little effect on the volume or frequency of the infant’s stools which were watery, offensive, and passed 7 to 11 times per day. His weight was 4·5 kg at 16 weeks.

One week after a dosage of 18 mg/day had been reached the infant became hypoesthetic, peripherally ‘shut down’, and grey and suffered a generalised convulsion lasting 3 minutes that was controlled with intravenous diazepam. After the convulsion he remained irritable and subconvulsive with increased muscle tone in all limbs, brisk tendon reflexes, and writhing movements when disturbed. Both pupils were constricted, the anterior fontanelle soft, his temperature 35·5°C, respiratory rate 20, and pulse rate 90 per minute. Full biochemical and bacteriological screens were negative. He was treated with intravenous gentamicin, fluocoxacinil, and metronidazole for 3 days, and given a single intravenous dose of pyridoxine 12 hours after the convulsion. Oral loperamide was stopped. For 24 hours after the convulsion he was irritable, subconvulsive—especially when disturbed, hypothermic, and unwell, but he made a full recovery and has had no further convulsions since withdrawal of loperamide. He is now 9 months old, has 1 to 2 bowel actions per day, and is growing well on oral Wysoy and a mixed lactose free diet. He is developmentally and neurologically normal with a weight of 6·4 kg.

In 1981 Friedli and Haenggeli described a 4 month old infant who suffered opiate like toxic effects, reversed by naloxone, after a single accidental overdose of 10 mg (3 mg/kg) loperamide3 and the signs exhibited by our infant were similar to those described. The dose of loperamide taken by our patient at the time of his convulsion was 4 mg/kg/day, actual body weight. We suggest that caution should be observed when prescribing loperamide in this dosage range, and that opiate like poisoning be included with ileus as a potential adverse effect of loperamide.

References


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Dr Sandhu and co-workers comment:

We were interested to read the letter of Weaver, Richmond, and Nelson, and agree that the symptoms in the patient that they describe were probably caused by the high doses of loperamide used. As we have previously stated, the drug should be used with caution particularly in sick infants.

There are, however, a number of points which should be borne in mind. First, in patients with life threatening protracted diarrhoea loperamide can be dramatically effective. Secondly, over 95% of an oral dose is metabolised during its ‘first pass’ through the liver and this process renders the drug virtually non-toxic to the central nervous system. Thus in theory loperamide in large doses could be toxic in patients with liver dysfunction, and in this context it would be important to know whether liver function was impaired in the patient reported by Weaver et al. Thirdly, since loperamide is an
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