DRUG REACTIONS AND INTERACTIONS

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Risks of diazepam treatment in acute neurological injury

Eldridge and Punt[1] from the Department of Neurosurgery, University Hospital, Nottingham, UK, have found that benzodiazepines are used inappropriately, often with risk to patients who have head injuries, spontaneous intracranial haemorrhages, or other neurological conditions. They have tabulated the details of 10 cases (aged 6-75 years) who presented to their unit over 18 months with complications after receiving i.v. diazepam. They report in detail on three of these patients.

Case 1. A 66-year-old man, who was an alcoholic and drank in excess of one bottle of spirits per day, presented to a casualty department after falling in his bathroom and becoming unconscious. On arrival he was disorientated in time and place; skull radiographs showed a left parietal skull fracture. He then had three generalised seizures which were self-limiting and he recovered consciousness between each seizure. He was given 10mg diazepam i.v. for each attack. He became unconscious again and had a respiratory arrest, which necessitated emergency ventilation and transfer to the neurosurgery unit. He was given phenytoin i.v. followed by maintenance treatment and he was extubated 24 h later without problems.

Case 2. A six-year-old girl was admitted to neurosurgery after being hit by a car. She had received a head injury and became unconscious. Computed tomography showed intracerebral contusions and features of raised intracranial pressure. Hypothermia (32°C) and hyperventilation with sedation were started, to control the pressure. These measures were continued for three days and then reversed sequentially while intracranial pressure was monitored. After reversal of the sedation, she was alert but unable to breathe or move her arms and legs. Radiographs of the cervical spine, a computed tomogram of the head, and results of magnetic resonance imaging were all normal. Concussion of the high cervical cord was diagnosed and over the next few days she recovered enough function of the spinal cord to breath and was gradually taken off the ventilator.

She then had a self-limiting generalised seizure and was treated with 3.75 mg diazepam i.v. She had respiratory failure and required ventilation for a further 48 h. She was then given loading and maintenance doses of phenytoin and no further fits occurred.

Case 3. A 32-year-old miner was struck on the head by a piece of machinery and became unconscious. On arrival in casualty he responded to verbal commands and was extremely agitated although breathing adequately. He was given 10 mg diazepam i.v. so that his extensive scalp lacerations could be sutured. His level of consciousness deteriorated rapidly and he developed respiratory failure which required emergency intubation and ventilation. He required ventilation for 48h and thereafter made a good recovery.

Eldgridge and Punt have commented that, although with their 10 cases many factors could be blamed for the deterioration of the patients' condition, in all cases diazepam was given inappropriately and was likely to be harmful. In their hands, seizures were controlled with phenytoin with a success rate equal to that obtained with diazepam and neither respiratory depression nor depression of the level of consciousness were problems.

Reference
1. Eldridge, P.R. and Punt, J.A.G. (1990). Risks associated with giving benzodiazepines to patients with acute neurological injuries. Br. Med. J. 300, 1189-1190.

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Colonic ulceration and bleeding with diclofenac

Carson et al,[2] from St. Peter's Hospital, Albany, NY,USA, have reported the development of colonic ulcerations in two women after the initiation of diclofenac therapy. The first of these patients, aged 60 years, was prescribed diclofenac (50 mg three times daily) for osteoarthritis. Her other medications were chlorpropamide, triamterene-hydrochlorothiazide, clonidine, amitriptyline and ferrous sulphate. After four months of diclofenac treatment, she was found to have positive stool tests of occult blood, and her haematocrit had decreased from 0.37 to 0.29. Oesophagogastroduodenoscopy revealed minimal antral gastritis. Colonoscopy showed

an ulcer in the ascending colon and several superficial ulcerations in the region of the hepatic flexure. A biopsy of the colonic mucosa showed focal necrosis and an acute inflammatory infiltrate. Diclofenac was stopped and she was started on sulindac (200 mg twice daily) and sucralfate (1 g four times daily). A second colonoscopy three months later showed no ulcerations.

The second patient, aged 67 years, was prescribed diclofenac (75 mg twice daily) for rheumatoid arthritis. She was also taking ranitidine and gemfibrozil every day and aurothioglucose once a month followed by prednisone for three days. After two months of diclofenac she was found to have positive stools for occult blood. Her haemoglobin level had decreased from 8.3 to 7.8 mmol/l. Oesophago-gastro-duodenoscopy revealed minimal antral gastritis, and colonoscopy showed ulceration of the caecum and ascending colon. Results of a colonic biopsy were consistent with an ulcerative process. The patient continued to take diclofenac and was started on sucralfate (1 g four times daily). One month later, she still had positive stools of occult blood; the diclofenac was then stopped and ibuprofen substituted. Subsequent stool tests were negative, and her haemoglobin level increased to 8.4 mmol/l.

A review of the literature by the authors of this report gave no evidence of caecal or colonic ulcerations associated with diclofenac. They commented that the possibility of colonic ulcerations should be considered in patients with gastrointestinal bleeding who are receiving diclofenac.

Reference

2. Carson, J., Notis, W.M. and Orris, E.S., (1990). Colonic ulceration and bleeding during diclofenac therapy, N.Engl. J. Med. 323,135.

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Life-threatening diarrhoea after misoprostol use

Kornbluth et al.[3], from the Mount Sinai Medical Center, New York, NY, USA, have reported a case of a patient with unrecognised Crohn ileocolitis who developed a nearly fatal secretory diarrhoea after short-term use of the prostaglandin E analogue, misoprostol.

The patient, a 56-year-old woman, was admitted to hospital with profuse diarrhoea, obtundation, and shock. She had been treated with naproxen, 400 mg four times daily, for eight weeks for symptoms of osteoarthritis. Two days before her admission, she started taking misoprostol (200 μg four times daily) because of a history of a bleeding ulcer while on another non-steroidal anti-inflammatory drug (NSAID). She took a total of six doses of misoprostol and then began passing voluminous watery, non-bloody diarrhoea. She required 7 l of normal saline to restore her systolic blood pressure from 76 to 100 mm Hg and was treated with clindamycin and aztreonam. Her large-volume diarrhoea persisted for the first two hospital days, despite the fact that she had no oral intake. On hospital day 9, colonoscopy showed severe cobble-stoning and linear ulcerations consistent with Crohn disease, extending from the distal transverse colon proximally and continuing into the terminal ileum. She admitted to treatment for 'Eisenhower disease' (Crohn disease) and terminal ileitis some 27 years earlier, for which she had received treatment for several months, although there was no follow-up afterwards. The disease had remained quiescent, until the present episode.

After her secretory-type diarrhoea resolved over the first five hospital days, she had five to six loose bowel movements daily, that were associated with abdominal cramping. Over the next two months, she was treated with sulphasalazine and oral ciprofloxacin and the Crohn disease-related symptoms resolved.

Diarrhoea occurs in 4-13 per cent of patients treated with misoprostol through several mechanisms although in a review of 2272 patients treated with the drug only four had to stop taking the drug because of diarrhoea[4]. The authors of the present report were of the view that misoprostol unmasked and exacerbated ileocolitis that had been long quiescent in their patient; they could not, however, exclude the possibility that naproxen, used concomitantly, had contributed to this flare-up, although the patient had tolerated several previous regiments of NSAIDs without diarrhoea and had been on a NSAID for two months before the present illness, whereas a total of only six doses of misoprostol was followed by the near fatal diarrhoea. They cautioned against the use of misoprostol in patients with known inflammatory bowel disease.

References

3. Kornbluth, A., Gupta, R. and Gerson, C.D. (1990). Life-threatening diarrhea after short-term misoprostol use in a patient with Crohn ileocolitis. Ann. Intern. Med. 113, 474-475.

4. Hertig, R.I. and Clay, G.A. (1985). Overview of clinical safety with misoprostol. Dig. Dis. Sci. 30, 1855-193S.

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