CORRESPONDENCE

INHALATION ANAESTHETICS AND INVERTEBRATES

Sir,—The communication of McKenzie and his colleagues [1] brings to mind a conversation I had recently with Professor J. Yule Bogue concerning the early history of halothane.

Professor Bogue, now in his mid 80s, is still active in the pharmaceutical industry and living in Portola Valley, California. He was intimately involved in drug research and manufacture immediately following the Second World War, as Joint Managing Director of the Pharmaceuticals Division, Imperial Chemical Industries Ltd (see [2]).

He described attempts by I.C.I. to preserve stored grain (invertebrates) were not killed, but anaesthetized by the vapour. Twelve halogenated hydrocarbons were then synthesized and tested for toxicity in dogs (vertebrates). Eleven were highly cardiotoxic at anaesthetic concentration, but the twelfth had a satisfactory therapeutic index and was subsequently named halothane.

It seems the wheel has completed a full turn.

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PERSISTENTLY INCREASED MORPHINE-6-GLUCURONIDE CONCENTRATIONS

Sir,—A 17-yr-old girl was admitted to our regional neuroscience intensive therapy unit (ITU) with acute inflammatory polyneuropathy (Guillain Barré syndrome) requiring artificial ventilation. Analgesia was provided by an i.v. infusion of morphine 2-10 mg h⁻¹. Sedation was provided initially by midazolam 5-15 mg h⁻¹, which subsequently was changed to propofol 100-250 mg h⁻¹. A feature of this girl’s management was the consistently high level of sedation required.

Throughout the course of her illness she suffered recurrent staphylococcal chest infections which were treated with flucloxacinill, and an episode of pseudomembranous colitis, treated with vancomycin. Renal function remained normal.

Morphine was discontinued 40 days after admission to ITU. Propofol was also stopped at this time and lorazepam 2 mg orally twice a day was commenced. Her subsequent course was complicated by a grand mal fit, thought to be the result of morphine withdrawal, and allodynia, thought to be a feature of a remyelination process.

Plasma morphine and metabolite concentrations were measured by high pressure liquid chromatography [1, 2] 19 days after discontinuation of the infusion. Results were as follows: morphine-6-glucuronide (M6G) 125 ng ml⁻¹; morphine-3-glucuronide (M3G) 70 ng ml⁻¹; morphine was not detected. Repeat measurements 10 days later showed no detectable morphine or M6G; M3G concentration was 21 ng ml⁻¹ of M3G.

These values raise some interesting points. First, M6G concentrations are persistently increased 19 days after discontinuing morphine, in the absence of impaired renal function [3]. This may be caused partly by enterohepatic circulation of M6G [4]. M6G is excreted in bile into the gut [5], where some may be metabolized further by bacterial glucuronidases. Alterations in bowel flora following antibiotic therapy may have resulted in an absence of these enzymes, and M6G may have been reabsorbed when bowel function resumed after discontinuation of the morphine infusion.

Second, the M6G:M3G ratio at the initial set of measurements is increased. Oxazepam inhibits M3G glucuronidation, possibly by competing for UDP-glucuronyl transferase [6]. Lorazepam is glucuronidated by the same enzyme and may have a similar effect.

The resulting prolonged increase in M6G concentrations has obvious implications for patients receiving morphine infusions, antibiotics and benzodiazepines.

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