second dose of suxamethonium was used. In others, there is a possibility that residual suxamethonium remaining in the tail of an indwelling needle has been flushed into the circulation or that the effects of other drugs or surgical stimulus have not been excluded. Nevertheless, we are sure that very rare idiosyncratic bradycardia may occur with suxamethonium. This is true of other drugs, and Dr Morgan in his reply to our original letter [1] pointed out the rare bradycardias of vecuronium (a drug which we do not use for Caesarean section—the competitive muscle relaxant in the early half of the series was alcuronium, while the one more recently used was atracurium). Despite this, the use of atropine has disappeared from routine anaesthetic practice in non-obstetric general anaesthesia.

In the series of 20 cases of bradycardia following suxamethonium that Dr Viby-Mogensen mentions [2] there are a number of interesting aspects. First, only one case involved Caesarean section, therefore the problem we address is not that which is particularly associated with Caesarean section. Second, as two of the patients had received atropine i.v. at induction, clearly, its use is of dubious value. Third, 18 of the 20 patients received fentanyl at induction, and this may have contributed to the problem; i.v. opioids are used rarely in obstetric anaesthesia. Fourth, despite their department's collection of a large number of cases, they still do not deem it necessary to administer atropine before operation.

The argument of our original letter is that, when atropine has been abandoned for routine use in general anaesthesia, there is even less indication for its routine use in obstetric anaesthesia. We stand by that position and feel that our large series supports this view.

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REFERENCES

HEPATOTOXICITY AFTER GENERAL ANAESTHESIA

Sir,—Hussey and colleagues [1] have recently reported evidence of liver damage following inhalation anaesthesia. Currently we are investigating postoperative hepatocyte injury using an alternative marker of liver disease, the serum F protein concentration. Although our preliminary results confirm that volatile anaesthetics are often associated with hepatic damage, we have found that the injury presents several days later than previously described. We have also observed a paradoxical improvement in hepatic function in patients with preoperative liver damage.

We have studied 12 previously healthy adults undergoing minor surgical procedures with uncomplicated inhalation anaesthetics (10 received halothane, one received enfurane and one received isoflurane). The postoperative serum F protein concentration (measured 24 h after surgery) did not change significantly (paired t test) from preoperative values. The serum F protein concentration is a very sensitive test of liver damage; it shows a close correlation with the histological assessment of hepatocellular damage, and the concentration is increased in patients such as the elderly who have minimal hepatic disease (unpublished data). Our failure to confirm the occurrence of early postanaesthetic liver damage may result from the small number of patients studied and the relatively insensitive statistical techniques used. However, it may indicate that postoperative changes in GST represent enzyme induction rather than hepatocellular damage.

Previous studies of postoperative liver damage have found evidence of hepatic injury several days after exposure [2]. We have studied 22 patients, receiving uncomplicated inhalation anaesthesia 6 days after exposure. In the 15 patients with normal preoperative liver function (serum F protein concentration < 60 mg ml−1) the serum F protein concentration was increased after operation in 10 and this change was observed with all anaesthetic agents studied (fig. 1, top graphs). In seven patients with preoperative liver disease (serum F protein concentration > 60 mg ml−1) there was a significant decrease in the postoperative serum F protein concentration (measured 24 h after surgery) compared with normals.

FIG. 1. Top graphs: Serum F protein concentration (log scale) before and after operation (day 6) in patients receiving inhalation anaesthetic agents. Patients with preoperative liver disease (lower graphs) were suffering from drug induced liver disease (two), alcohol abuse (one), carcinoma (one) or had no known cause of liver damage (two). Broken lines indicate upper limit of normal for serum F protein concentration. • = Halothane; ▲ = isoflurane; ■ = enfurane. + ● = Two inhalation anaesthetics used during the same operation.
POTENTIAL PROBLEMS OF USING BOTH OPIOIDS AND LOCAL ANAESTHETIC

Sir,—We are taught that opioids cause respiratory depression, and indeed they do, both in volunteers who are not in pain and in pain-free animals. In practice, significant postoperative clinical respiratory depression is not a common problem when opioids are titrated against pain. The reason for the difference between the experimental and clinical contexts is the presence or absence of pain. Those working in the field of chronic pain are aware of this difference. Patients taking appropriate doses of oral morphine for management of opioid-sensitive pain are troubled by constipation, not by respiratory depression. A patient taking opioids (without respiratory depression) whose pain is then relieved by another measure, such as a neuolytic block, will succumb to respiratory depression unless the dose is reduced [1]. After successful procedures, it is important to reduce the opioid for this reason [2].

Where opioids are used in postoperative care, there are several situations in which ignorance of this balance between pain and dose of opioid has the potential for disaster. If a patient who has been given opioids without satisfactory pain relief, but with no clinical respiratory depression, is subsequently given extradural local anaesthetic (or local anaesthetic by any other route), the balance between pain and those earlier doses of opioid is altered, and clinical respiratory depression may occur.

Intrathecal opioids used for perioperative pain relief are administered commonly at induction rather than titrated against pain. The optimum dose may vary and, unless dose–response relationships are understood, the dose given may be excessive. If the local anaesthetic results in good pain relief while using local anaesthetic and opioid simultaneously, there is no pain to balance the dose of opioid. The widely quoted respiratory depressant effect of intrathecal opioids [3] involved just such a local anaesthetic–opioid mixture.

In the unfortunately common situation where use of extradural local anaesthetic cannot be continued for logistic reasons, absorption of opioid from i.m. injection may be delayed if the injection is given into muscles still "covered" by the extradural. In patients receiving a lumbar extradural block and a gluteus maximus injection, the time of the mean peak plasma morphine concentration was 90 min \((n = 10)\) [4], compared with a mean time of peak concentration of 15 min \((SEM\ 2.3)\ (n = 5)\) [5] after deltoid injection of 10 mg in volunteers. Such delayed absorption (and effect) is analogous to that in the shocked patient in whom i.m. injection results in a reservoir of drug which is released when muscle blood flow increases.

The clinical message is that the dose of opioid should be titrated against pain.

REFERENCES