INCREASED TOXICITY OF ALTHESIN IN NEWBORN ANIMALS

Sir,—A recent article (Downing, Coleman and Meer, 1973) on the use of Althesin for obstetric anaesthesia concluded that, while it was satisfactory for the parturients undergoing Caesarean section, the newborns often showed a significant degree of neonatal depression. This report and earlier observations of Soyka, Gyermek and Campbell (1970) on the high toxicity of other potent steroid anaesthesics to newborn rats prompted this study on both rats and mice.

Newborn (1-day-old), 3-day-old and 21-day-old Wistar albino rats were injected s.c. and i.p. with increasing doses of Althesin. For the newborn and the 3-day-old groups the steroid preparation was diluted with normal saline and the injected volume varied between 0.05–0.15 ml. For the 21-day-old group Althesin was given undiluted. Acute toxicity was observed within 5–10 min of the administration. The LD 50 of Althesin was found to be 1.5 ml/kg (i.p.) and 1.66 ml/kg (s.c.) for the 1-day-old rats (which corresponds to 18 and 20 mg/kg respectively of the active steroid ingredients) and 5.8 ml/kg (s.c.) for the 3-day-old rats. In contrast the minimal lethal dose in the 21-day-old rats was 15 ml/kg (i.p.) and 32 ml/kg (s.c.). Thus the acute toxicity, dependent on the route of administration, was 10–20 times higher in the newborn than in the young adult rats, and seemed to diminish gradually during maturation.

Marked difference in acute toxicity between newborn and young adult rats was also found with pregnenolone and pregnanediol, two other potent steroids, with hypnotic properties (Soyka, Gyermek and Campbell, 1970). Progesterone, which exhibits only weak hypnotic action, likewise produced increased toxicity in newborn mice (Karnofsky, Hamre and Hysom, 1952) and rats (Soyka, Gyermek and Campbell, 1970). Increased uptake into the brain, lower brain threshold and decreased metabolism all contributed to the high toxicity of pregnenolone in the newborn (Soyka, Gyermek and Campbell, 1970). It is possible that the same factors may be responsible for the pronounced sensitivity of newborn animals to Althesin. It is worthwile to note that most pharmacological agents do not exhibit such a degree of age-dependent changes in toxicity.

Additionally, pregnant mice were injected with Althesin 1 ml/kg (12 mg/kg active ingredient) i.v. which is approximately 1/4 of the LD 50 dose. The animals were treated at 8–12 hour intervals during the last 1–3 days of pregnancy and were kept under observation during daytime. If the onset of the deliveries could be observed and, providing the animal was delivering living pups, an additional dose of Althesin 1 ml/kg was injected. The remainder of the deliveries was closely observed.

Four out of 5 animals, which delivered during the observation period, produced living pups. In 3 animals which were injected also during delivery the pups born prior to the injection were all alive. Most of those born following the administration of Althesin were dead on delivery or died within an hour. The pattern of toxicity in 1 animal was characteristic: Althesin was given following the delivery of 4 healthy pups and the next 2, born within 10 min of the administration, were dead. Of the last 3 pups born within the next half an hour one died.

In keeping with our observations, Child and associates (1972) noted that if pregnant rats and mice received intravenous doses of Althesin during the last days of pregnancy, but not immediately prior to delivery, the newborn animals were in good condition and matured normally. The effect of Althesin during labour was not reported.

The radioautographic studies of Card, McCulloch and Pratt (1972) have shown that only a small portion of the injected alphaxalone or alphadolone (the active ingredients of Althesin) enters the foetal circulation in the rat, but the radioactivity, indicating the presence of the steroid (or its metabolites) disappears within 30 min. The survival of some newborn mice in our study, which were born more than 15 min following the injection of Althesin to the mother, seems to be in accordance with the radioautographic data.

The above observations indicate that foetal toxicity to Althesin in utero is not as significant as in the newborn, provided that sufficient time elapses to allow rapid maternal metabolism of the agent. The data suggest the use of extreme caution in administering Althesin to obstetric patients until a lower dose regimen or different timing of administration is established. Based on the rapidly declining plasma and brain levels of Althesin (Card, McCulloch and Pratt, 1972; Child et al., 1971) a single induction-dose of this agent for Caesarean section might be acceptable; but this dose should not be followed by additional maintenance doses, which may be given close to the moment of delivery. It is obvious that further study of the metabolism of this new anaesthetic agent on newborn and pregnant animals is required. The above observations, in addition, may indicate that Althesin does not enter the foetal circulation in the rat, but the dose range is established through carefully controlled pharmacological studies on this presumably susceptible age group.

LASZLO GYERMEK
Portola Valley, California

REFERENCES

BACTERIOLOGICAL FILTERS FOR STRAIN GAUGES
Sir,—Whenever strain gauges are used in a clinical environment, there is a problem of keeping them free from debris and of sterilization.
Bacteriological filters are clinically effective in preventing the transmission of infection. We investigated the effect of a filter on the response of a strain gauge transducer with the idea that it might be used to prevent transmission of matter from the transducer to the patient and of blood from the patient to the transducer.

A filter that will allow bidirectional fluid flow is required in order to avoid rectification of the pressure wave passing through it. An appropriate type is the Millex 13, 0.22 μ pore size (Millipore Ltd) with a support screen (XX3001210) on the upstream side.

We compared the mechanical responses obtained from a sinusoidal pump driving a transducer (Micron Ltd) and three-way tap in series with those from the system with the addition of a filter (fig. 1). We derived the frequency response curves from the output from the transducer (fig. 2).

We then tested the step responses of the two systems by puncturing a balloon on the three-way tap. From the step response curves (figs. 3, 4), we derived the following data:

<table>
<thead>
<tr>
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<th>Strain gauge alone</th>
<th>With filter</th>
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<tbody>
<tr>
<td>Logarithmic decrement (λ)</td>
<td>1.87</td>
<td>1.56</td>
</tr>
<tr>
<td>Hydraulic damping (β)</td>
<td>0.285</td>
<td>0.242</td>
</tr>
<tr>
<td>Oscillation period (τ)</td>
<td>20</td>
<td>22.5</td>
</tr>
<tr>
<td>Natural frequency (f₀)</td>
<td>52</td>
<td>46</td>
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Where \( \lambda = \ln \frac{q_1}{q_2} \) where \( q_1, q_2 \) are the values of the peaks of two successive cycles of the step response.

\[
\beta = \frac{\sqrt{4\pi^2 + \lambda^2}}{2\pi \tau}
\]

We therefore conclude that placing a Millipore filter in series with a strain gauge as described has a clinically insignificant effect on the transducer response, and suggest that this method could be used to obviate the tiresome problem of sterilizing strain gauges in clinical use.

J. A. LACK
Farnborough, Kent
M. LIVERANI
Stanford, California, U.S.A.

MALIGNANT HYPERPYREXIA CAUSED BY TRIMEPRAZINE

Sir,—I was a little surprised by the title of the report of Moyes, D. G. (Br. J. Anaesth. 1973, 45, 1163), “Malignant Hyperpyrexia caused by Trimeprazine”. There was no evidence presented in this report which would have indicated clearly that the drug reaction was identical with the syndrome which we call malignant hyperpyrexia.

In individuals with malignant hyperthermia there is a high resting serum-c.p.k. level before exposure to anaesthetic agents, and a dominant inheritance of the myopathy responsible for c.p.k. leakage also reveals this anomaly