Studies of Epontol

Dr. Doenicke has sent the following reply to the letter from Dr. J. Selwyn Crawford which was published in the September issue of the Journal (page 713).

Sir,—The criticism of our paper concerns that part of our studies dealing with the use of Epontol in obstetrics. We ourselves had stated that these were preliminary results (see page 419). The essential objective of the article was the course of the propandid concentration in human serum in connection with the influence of the serum cholinesterase on the breakdown of propandid.

Experiments are unjustifiable on patients in a situation such as parturition. It is impossible to follow up the course of their concentrations continuously.

Our experiments were concentrated on volunteers in whom disturbances as a result of stress or variations in basic autonomic condition are less likely.

In obstetrics initially we followed the manufacturer's dosage recommendations and gave on average 500 mg (7-10 mg/kg body weight in cases I and VII of table II, upper part). With experience we found that on average doses of only 250 mg (3-4 mg/kg body weight in cases I-IV, lower part of table II) were necessary to induce anaesthesia. The doses administered to each individual were later calculated on the basis of mg/kg body weight in order to obtain comparable values for easier reference. Thus, for all cases summarized in table II a range between 3 and 9 mg/kg is noted. A linear correlation between serum concentration and dose injected per kg body weight was not expected. An established fact is that in maternity cases the serum cholinesterase is reduced and therefore a small dose of Epontol is required.

As we pointed out in our report, interpretation of the results with regard to placental passage demands reservation. To Epontol with a molecular weight of 337 the placenta offers no barrier. After relatively quick injection of a large dose (patients I-IX) the active compound passed very quickly from the maternal into the cord blood. This may be explained by the low rate of protein binding for Epontol. The stated four results certainly cannot prove the balance of concentration in the 3rd minute. The hypothesis derived from the preliminary studies (page 419), however, was fully confirmed by further examinations in vivo and on isolated placenta in vitro. (We are preparing a full report on this.)

The writer's critical discernment of the extremely high value of 11.9 µg/ml in column 3, table II, motivated him to doubt the calculation of the mean value. This is justified. We had abstained from describing this case in detail since a discussion of it would have exceeded the scope of our paper. This woman received the Epontol in two portions by fractional injection. Initially the patient was given Epontol 200 mg at the start of a uterine contraction. Due to the protracted course of the delivery a further 200 mg was injected 30 seconds later immediately after a contraction of the uterus. The passage of Epontol was accelerated. Not only uterine contraction but also psychic factors, circulatory disorders, and premedicants which inhibit the serum cholinesterase, play a great role in it.

In the comparison of the maternal serum cholinesterase activity and the concentration in the cord blood the body weight was not taken into account in the criticism. If in the presence of 107 serum cholinesterase activity and 62 kg body weight, a 200 mg/kg propanidid dose is administered, then 4.03 mg/kg body weight Epontol is a relatively high amount. In such circumstances the cord blood concentration must be expected to be relatively high. On the other hand, in the presence of 64 serum cholinesterase activity and 85 kg body weight (table II) 2.9 mg/kg Epontol is low. It follows that enzymatic splitting in the blood is delayed. The supply of active compound is relatively high for the low enzyme activity. Passage into the cord blood is accelerated and, understandably, a higher value was obtained after 2 minutes in this case (3.9 µg).

We reported that Epontol diffuses very quickly into tissues. The greatest role in the degradation of propanidid is played by the serum cholinesterase. Enzymatic activity is lower in the cord blood than in the maternal blood as was found by investigations the results of which were not included in the present publication. Referred to the total volume of placental tissue the serum cholinesterase activity is high in the placenta, but per ml it is lower than in the maternal blood. The enzymatic activity in the placental tissue reduces the propanidid concentration in the foetal circulation, but does not suffice to hydrolyze the offered substrate completely. However, this situation only applies in the case of rapid injection of large propanidid doses (7-10 mg/kg body weight). The additional breakdown of propanidid in the placenta is an essential advantage over the barbiturates.

While the article was in the press the preliminary findings were confirmed by subsequent investigations, and therefore we thought it correct not to change the report of the preliminary study.

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