References

Aballi, A. J., Banus, V. L., De Lamerens, S., and Rosengvaig, S. (1959). *American Journal of Diseases of Children*, 97, 524.
Ahuja, G. L., Willoughby, M. L. N., Kerr, Margaret M., and Hutchison, J. H. (1969). *British Medical Journal*, 3, 743.
Balfour, H. H., jun., Block, S. H., Bowe, E. T., and James, L. S. (1970). *American Journal of Obstetrics and Gynecology*, 107, 288.
Barrow, E., and Peters, R. L. (1968). *South African Medical Journal*, 42, 265.
Beard, R. W., Morris, E. D., and Clayton, S. G. (1966). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 73, 860.
Bonnar, J., McNicol, G. P., and Douglas, A. S. (1971). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 78, 355.
British Medical Journal, 1971, 4, 1.
Chadd, M. A., Elwood, P. C., Gray, O. P., and Muxworthy, S. M. (1971). *British Medical Journal*, 4, 516.
Chamberlain, G., and Fosker, A. P. (1970). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 77, 1096.
Evans, A. R., Forrester, R. M., and Discombe, C. (1970). *Lancet*, 1, 517.
Hull, M. G. R., and Wilson, Judith, A. (1972). *British Medical Journal*, 1972, 4, 321.
Kozinn, P. J., Ritz, N. D., Moss, A. H., and Kaufman, A. (1964). *American Journal of Diseases of Children*, 108, 413.
Kozinn, P. J., Ritz, N. D., and Horowitz, A. W. (1965). *Journal of the American Medical Association*, 194, 567.
Kubli, F., Berg, D., Köhnlein, G., Hüter, J., and Bretz, D. (1967). *German Medical Monthly*, 12, 315.
Lanzkowsky, P., Joffe, H. S., Levy, S., Nossel, H. L., and Mibashan, R. S. (1967). *South African Medical Journal*, 41, 1039.
Leonard, S., and Anthony, B. (1961). *American Journal of Diseases of Children*, 101, 170.
McDonald, J. S. (1967). *American Journal of Obstetrics and Gynecology*, 97, 912.
Markarian, Marguerite, Cohen, R. J., and Milbauer, B. (1971). *Journal of Pediatrics*, 78, 74.
Mountain, K. R., Hirsh, J., and Gallus, A. S. (1970). *Lancet*, 1, 265.
Nelson, G. H., Wages, H. S., Hahn, Dorothy, A., Aziz, E. M., and Freedman, D. S. (1971). *American Journal of Obstetrics and Gynecology*, 110, 737.
Pachman, D. J. (1962). *Pediatrics*, 29, 907.
Robinson, R. J., and Rossiter, Mary A. (1968). *Archives of Disease in Childhood*, 43, 684.
Saling, E. (1965). *Journal of the International Federation of Gynaecology and Obstetrics*, 3, 100.
Valentine, G. H. (1964). *Canadian Medical Association Journal*, 91, 177.
Van der Horst, R. L. (1963). *Archives of Disease in Childhood*, 38, 280.

Massive Scalp Haemorrhage after Fetal Blood Sampling Due to Haemorrhagic Disease

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Summary

Massive subaponeurotic haematoma occurred in a baby after suture of bleeding scalp blood sampling stabs made before delivery. Eighteen hours after delivery blood samples showed marked prolongation of the prothrombin time. The condition was successfully treated with vitamin K_1 and blood transfusion.

Introduction

Haemorrhagic disease of the newborn (*British Medical Journal*, 1971) is usually the result of a dietary deficiency of vitamin K in breast-fed babies and seldom occurs less than a few days after birth. A unique example, however, is described below, believed to be the first reported case of proved haemorrhagic disease complicating fetal blood sampling in labour.

Case Report

The mother was a healthy 30-year-old Negress who had one previous baby without complication and a normal second pregnancy. Labour occurred spontaneously in the 42nd week in February 1971. Progress was accelerated by forewater rupture at 5 cm dilatation of the cervix and she delivered normally six hours later after a short second stage. The amniotic fluid became lightly stained with meconium and a scalp blood sample was taken for measurement of pH, which was 7·26 (maternal 7·37). The bleeding was not unusually heavy but would not stop. Nevertheless, it was not sufficient to speed the fetal heart before delivery 40 minutes later.

Two scalp stabs had been made 1 cm apart over a parietal bone and at least 1·5 cm from the sagittal suture. The blade used was less than 2 mm wide and protruded 2 mm from the protective plastic shoulder.

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The baby, a boy, weighed 3,800 g and had an Apgar score of 10. He behaved normally at birth but continued to bleed slowly from the scalp stabs despite prolonged pressure over the area. After three hours the stabs were underpinned with three sutures of fine silk mounted on an atraumatic cutting needle. These stopped the visible bleeding and the baby seemed well, but nearly 15 hours later oozing recurred, his head was swollen, and he was very ill. He was shocked, had a slow heart beat, and his respiratory rate was 60/min. There was pitting oedema of the scalp overlying a generalized swelling which extended to the limits of the scalp and across all suture lines, typical of a huge haematoma beneath the epicranial aponeurosis. Eighteen hours after delivery blood was taken from the umbilical vein for coagulation studies. The prothrombin time was 110 seconds; the various results are given below. The haemoglobin was 8·7g/100 ml, and there was a pronounced metabolic acidosis, presumably due to blood loss and anaemia.

Subsequently vitamin K_1 (total 9 mg) and antibiotics were given, intravenously at first, and bicarbonate, dextrose, and electrolyte solutions were infused appropriately. Fresh blood transfusions totalling 240 ml were given within 48 hours of delivery. After the first 180 ml of blood the haemoglobin fell further to 7·6 g/100 ml, probably owing both to haemodilution and to continued bleeding into the scalp. The haemoglobin then rose rapidly to 10·7 g/100 ml (venous) on the fourth day, and 12·4 g/100 ml (capillary) on the twelfth. The prothrombin time at 42 hours was 40 seconds, at 48 hours 21 seconds, on the third day 18 seconds, and on the fourth day was normal, 15 seconds. After the first critical 48 hours the baby improved rapidly. He took feeds on the third day and behaved normally from the fourth. By the time he went home on the twelfth day there was only a little bogginess of the scalp and periorbital oedema. His progress at 12 months remained normal.

There are two additional clinical points worth noting. Firstly, the child's head circumference was 34 cm at birth and did not reach its maximum until the third day, when it was 39 cm, suggesting that bleeding continued long after treatment started. Secondly, he was never jaundiced. The highest serum bilirubin was 5·9 mg/100 ml after 42 hours.

The coagulation studies made at 18 hours were as follows: prothrombin time (one-stage method) 110 sec (control, 15 sec), partial thromboplastin time with kaolin 130 sec (control, 60 sec), platelets 174,000/mm^3, fibrinogen (semiquantitative measurement by thrombin titre using Fibrindex) titre 1/32 (control, 1/32); there was no excess of fibrin/fibrinogen degradation products. The gross prolongation of the prothrombin

time and partial thromboplastin time with kaolin indicate severe deficiency of vitamin-K-dependent factors, and this could not have resulted from disseminated intravascular coagulation because there was no deficiency of platelets or fibrinogen and no abnormal fibrinolysis. Though factors V and VIII were not tested, deficiencies can be excluded; they cannot have resulted from genetic or hepatic disorders, because of the duration and timing of the clotting defect, nor from consumption coagulopathy. The nature of the clotting disorder and response to treatment with vitamin K_1, even though blood was also given, make the diagnosis of vitamin K deficiency certain.

The mother had a normal prothrombin time two days after delivery, and other screening tests at six weeks showed no clotting defect.

Comment

This baby developed a subaponeurotic haematoma almost certainly due to the sutures causing or adding to vascular damage beneath the aponeurosis and sealing the stab sites. However, the bleeding began in labour, and the point is made that haemorrhagic disease can occur early enough to complicate fetal blood sampling. Though major complications of this procedure are rare fatal exsanguination in labour has been reported (Saling, 1965; Beard *et al.*, 1966), but adequate clotting tests were not possible in these cases. This baby luckily delivered soon after the blood sampling and yet nearly died because the diagnosis was not suspected. Earlier prophylactic infusion of fresh frozen plasma (Ahuja *et al.*, 1969) and reliance on local pressure rather than sutures to control the bleeding might have prevented such serious complication. The total dose of vitamin K_1 given in this case was much more than necessary, and 1 mg should always suffice.

A huge volume of blood can collect under the aponeurosis before it is noticed because of the symmetry and even distribution of the swelling. The possibility that much of this blood might be reabsorbed intact into the circulation was suggested by Robinson and Rossiter (1968) and is supported in this case by the rise in haemoglobin concentration that continued after transfusion and by the absence of jaundice.

We are indebted to Dr. P. J. N. Cox and Mr. A. C. Fraser for their kind permission to report this case, and to the Royal Society of Medicine, where it was first presented on 25 June 1971.

References

Ahuja, G. L., Willoughby, M. L. N., Kerr, Margaret M., and Hutchison, J. H. (1969). *British Medical Journal*, **3**, 743.
Beard, R. W., Morris, E. D., and Clayton, S. G. (1966). *Journal of Obstetrics and Gynaecology of the British Commonwealth*, **73**, 860.
British Medical Journal, 1971, **4**, 1.
Robinson, R. J., and Rossiter, Mary A. (1968). *Archives of Disease in Childhood*, **43**, 684.
Saling, E. (1965). *Journal of the International Federation of Gynaecology and Obstetrics*, **3**, 100.

Changes in Human Drug Metabolism after Long-term Exposure to Hypnotics

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Summary

The influence of the newer, non-barbiturate hypnotics Mandrax (diphenhydramine-methaqualone) and nitrazepam on drug-metabolizing capacity was assessed and compared with the effect of amylobarbitone, a known inducer of drug-metabolizing enzymes. Plasma antipyrine and phenylbutazone half-lives and urinary output of 6β-hydroxycortisol were used as indices. Volunteer subjects were exposed to therapeutic amounts of these agents and, in the case of Mandrax and barbiturates, further studies were carried out in dependent patients.

Mandrax but not nitrazepam increased the rate of drug metabolism, presumably by enzyme induction. The degree of induction was comparable with that produced by hypnotic doses of amylobarbitone. The Mandrax-dependent and barbiturate-dependent patients were the fastest metabolizers studied. It is concluded that drug interactions resulting from interference with drug metabolism are as likely to occur with Mandrax as with barbiturates. On the other hand, it is unlikely that such drug interactions would occur with nitrazepam.

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Introduction

As a group, hypnotic drugs are among the most widely used and are frequently prescribed in combination with other drugs. Since they may cause alteration in protein binding and in rate of metabolism of concurrently administered therapeutic agents, it is not surprising that there have been many reports of drug interactions occurring with this group (Hansten, 1971). With glutethimide, and to a greater extent with the barbiturates, the effects on drug metabolism are well documented (MacDonald *et al.*, 1969). Similarly, alteration in protein binding with chloral hydrate administration has been much studied (Sellars and Koch-Weser, 1971). In the present study we have examined the effects on drug metabolism of therapeutic doses of two of the newer, widely-used, non-barbiturate hypnotics, nitrazepam and Mandrax, together with the constituents of the latter, methaqualone and diphenhydramine. For comparison, we have also studied the effect of hypnotic doses of amylobarbitone, and in addition have measured the rate of drug metabolism in a few patients dependent on Mandrax or barbiturates. So far as we are aware, no formal assessment of the effects of these non-barbiturate hypnotics on human drug-metabolizing capacity has previously been made. However, in a recent study carried out in animals we have found Mandrax to have a potent inducing effect on liver microsomal enzymes, whereas nitrazepam even in high dose produced only a weak stimulation (Ballinger *et al.*, 1971).

In this investigation we have used plasma phenazone (antipyrine) and phenylbutazone (Butazolidin) half-life values together with urinary output of 6β-hydroxycortisol as indices of drug-metabolizing capacity. Both test drugs are extensively