strength solution, 0.2%, is given to children of 6 years and upwards. The strength of the solution is increased still further if hypotension can be maintained only with an excessive drip rate.

Results

Satisfactory hypotension was produced together with improved operating conditions in every case.

Five of the first 20 cases received procainamide because a suitably low blood pressure could be maintained only with an excessive drip rate. Since the use of stronger solutions of arfonad (in 24 cases) procainamide has not been given.

There was no operative death in the series. One child, aged 4 (who had thyroidectomy for thyrotoxicosis), died within 24 hours of operation from acute heart failure, having been extremely well post-operatively, and talking to a nurse a few minutes before her death. One of the infants caused temporary alarm during the operation when the pulse became imperceptible owing to the drip being accidentally accelerated.

Blood loss was replaced whenever considered necessary (three cases).

In only two cases was a vasopressor drug used; this was given to raise the blood pressure quickly to identify and control bleeding-points before closing the dura mater. In all the other cases the blood pressure returned to near normal levels within a few minutes of stopping the arfonad and levelling the table.

Summary

A series of 44 children is presented in which surgery was performed under controlled hypotension induced by arfonad. An analysis of these cases is shown in tables.

It is concluded that controlled hypotension can be used in paediatric surgery, when indicated, with no greater danger than in adult surgery.

The tolerance of the child raises certain problems in technique of administration, which are described.

The value of the flexibility of action of arfonad when given by drip transfusion is emphasized.

My thanks are due to Mr. Wylie McKissock, Mr. D. Innes Williams, and Mr. George MacNab for permission to record the cases on which this report is based, and to Roche Products Limited, who kindly supplied the arfonad.

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It was a hundred years ago that JOHN SNOW, well known as an anaesthetist, asserted that a cholera epidemic raging in London would cease if the handle of a pump in Broad Street (now Broadwick Street), Soho, were removed. He was gathering evidence that cholera is a water-borne disease, and found that all the infected persons in this epidemic had drawn water from the Broad Street pump. The epidemic, which had caused 500 deaths in 10 days, stopped immediately the pump was put out of action. Hard by where the pump once stood is now a public house, and, in response to a request that this landmark in epidemiology should be commemorated, the owners, Messrs. Watney, Combe, Reid and Co., agreed to change its name from the "Newcastle On Tyne" to the "John Snow." The occasion was celebrated on July 5 when Professor BRADFORD HILL, F.R.S., before a gathering of epidemiologists, recalled these events and unveiled the new inn sign depicting John Snow. Some mementoes of Snow are now on permanent view at the premises.

THE POTENTIATION OF BARBITURATE ANAESTHESIA BY DINITRO-*O*-CRESOL

BY

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Our attention was recently drawn to the findings of Bain (1952) and Brody and Bain (1954) that a wide range of barbiturate drugs exhibit *in vitro* dissociating effects on oxidative and phosphorylating processes in liver and brain mitochondria, qualitatively similar to, although quantitatively less than, those produced by dinitrophenol (D.N.P.). Bain also stated in a footnote that barbiturate anaesthesia in rats and mice was potentiated by dinitrophenol, while Brody and Bain showed that the effects of thiobarbiturates on mitochondrial preparations more closely resembled those of D.N.P. than did those of oxygen barbiturates.

The widely used agricultural herbicides dinitro-*ortho*-cresol (D.N.C.) and dinitro-*sec*-butylphenol (D.N.B.P., "dinoseb") have a mode of toxic action almost indistinguishable from that of D.N.P., and are sufficiently hazardous in agricultural usage to present a distinct possibility of occupational poisoning. Sedation by oral or parenteral barbiturates has hitherto been advised to allay any dangerous restlessness or excitement which may occur in such cases (Bidstrup and Payne, 1951; B.M.A., 1951; Martindale, 1952; Edson, 1955). There also exists the possibility that a case of mild or even severe D.N.C. intoxication may require the induction of surgical anaesthesia for some essential operative procedure, such as the treatment of physical injuries. A series of experiments has therefore been carried out to compare the responses of normal and D.N.C.-poisoned animals to the narcotic effects of six representative barbiturates.

Materials and Methods

The animals used were adult male and female albino rats of Glaxo-Wistar strain, acclimatized to our laboratory conditions (67–76° F. (19.5–24.5° C.) during the experimental period) and maintained on M.R.C. Diet No. 41. D.N.C. was administered intraperitoneally as a 1% solution of the sodium salt, the dose mainly used (17–20 mg./kg.) being that known from previous work to cause moderate to severe D.N.C. poisoning with an expected 20–30% mortality, under our experimental conditions. (In order to maintain a direct check on this point, a "D.N.C. control group" was included in all but one of the trials. The mortality in these 48 animals was 29%.)

The oxygen barbiturates investigated were pentobarbitone ("nembutal," intraperitoneally), hexobarbitone ("cyclonal," intravenously), amylobarbitone ("amytal," i.v.), and phenobarbitone ("gardenal," i.v.), the thiobarbiturates being thio-pentone ("pentothal," i.v.), and thialbarbitone ("kemithal," i.v.). All were administered as freshly prepared solutions of the sodium salts, injections being carried out by one person, with due care to avoid any marked variation in the speed of injection into individual animals and in the experimental groups.

Preliminary trials with each barbiturate indicated the dosage likely to cause a degree of narcosis with a readily recognizable onset and duration. A state of deep flaccid "surgical" anaesthesia was sought in most trials, since

restoration of muscular tone and slight stirring movements on disturbances were then "end-points" comparatively easily recognized. With intraperitoneal pentobarbitone and with amylobarbitone, less deep degrees of narcosis were employed. Observations on onset, depth, and duration of narcosis were made by one observer. In general, the individual response among the controls for each barbiturate was so uniform that it was considered justifiable to use group mean times of onset and duration of narcosis in the comparisons.

Each barbiturate was investigated by comparing the effects of a "high" barbiturate dose in normal control animals and in animals suffering from moderate to severe D.N.C.-intoxication. The use of comparatively high dosages both of D.N.C. and of barbiturate was intended to simulate the use of the latter to induce surgical anaesthesia or to combat marked excitement in a case of D.N.C.-poisoning.

Further tests were then carried out on small groups of animals to determine if a reduced dose of intravenous thiopentone was significantly potentiated by a high dose of D.N.C., or if an anaesthetic dose of thiopentone was potentiated by an almost asymptomatic dose of D.N.C.

The experimental programme obviously did not cover the many possible variants of drug dosage and combination, and was carried out on only one species. Nevertheless the nature of the results obtained appears to justify early publication.

Results and Discussion

The accompanying Table gives details of the actual dosages of D.N.C. and barbiturate employed, group numbers and mortalities, approximate times of onset and duration of narcosis, and a summary of the conclusions drawn from each experiment.

The series showed clearly that, with the exception of hexobarbitone, the narcotic effect of the barbiturates tested was markedly potentiated by the presence of severe D.N.C. intoxication. Deeply anaesthetizing but normally non-fatal doses of both thiopentone and thialbarbitone were lethal in D.N.C.-poisoned rats. Most such animals developed deep cyanosis within seconds of thiobarbiturate injection, dying immediately or within a few minutes after respiratory and then cardiac arrest. Of the four oxygen barbiturates examined pentobarbitone, amylobarbitone, and phenobarbitone were all potentiated by D.N.C.-poisoning, as judged by the greater rapidity of onset, depth, and duration of their narcotic effects. Potentiation was not demonstrated with hexobarbitone under similar conditions. This observation may be explained by the finding of Brody and Bain that hexobarbitone ("evipan") caused appreciably less *in vitro* dissociative effect upon mitochondrial oxidative-phosphorylating processes than the other twelve barbiturates investigated by them.

The results obtained also suggested that barbiturate potentiation is only likely to occur with D.N.C. dosages high

Effects of Barbiturate Drugs in Normal and in D.N.C.-treated Rats

Compound (as Na Salt) and Route	Dose (mg./kg.)	No. in Group	% Mortality (7 Days)	Narcosis Produced*			Survival Times	Potentiation of Barbiturate Effects	Remarks
				Depth	Onset (min.)	Duration (min.)			
Phenobarbitone i.p.	20	12	0	Moderate	5-15	60-90	—		
D.N.C. i.p.	20	16	25	—	—	—	1-3 hrs.		
Phenobarbitone i.p.	20								
concurrently with D.N.C. i.p.	20	16	37	Deep	2-3	120-180	1-12 "	+	
Hexobarbitone i.v.	40	16	0	Deep	Immediate	20-30	—		No apparent influence of D.N.C. on barbiturate anaesthesia
D.N.C. i.p.	20	12	33	—	—	—	1-3 hrs.		
Hexobarbitone i.v.	40								
5-15 min. after D.N.C. i.p.	20	12	42	Deep	Immediate	20-30	1-2 "	—	
Amylobarbitone i.v.	60	8	37	Deep	3-5	180	1-2 hrs.		Dosage of both amylobarbitone and D.N.C. too high. Barbiturate after D.N.C. produced immediate cyanosis and prompt death in 4/7 animals. Survivors not cyanosed
D.N.C. i.p.	20	4	100	—	—	—	1-2 "		
Amylobarbitone i.v.	60								
5-15 min. after D.N.C. i.p.	20	7	57	Deep	1-1	180-300	1-20 min.	+	
Amylobarbitone i.v.	40	4	0	Moderate to mild	10 (2)	25 (2)	—		No cyanosis produced at these reduced dosages
D.N.C. i.p.	17	4	0	—	—	—	—		
Amylobarbitone i.v.	40								
5-15 min. after D.N.C. i.p.	17	4	0	Deep	2-14	60-90	—	+	
Phenobarbitone i.v.	100	8	0	Deep	20	120	—		
Phenobarbitone i.v.	100								
5-15 min. after D.N.C. i.p.	20	8	12	"	10	240-360	20 min.	+	
Thialbarbitone i.v.	80	6	0	Deep	Immediate	20-35	—		Immediate cyanosis and rapid death after barbiturate in D.N.C.-treated group. No cyanosis after thialbarbitone alone
D.N.C. i.p.	20	4	25	—	—	—	—		
Thialbarbitone i.v.	80								
5-15 min. after D.N.C. i.p.	20	4	100	Deep	Immediate	Fatal	< 1 min.	++	
Thialbarbitone i.v.	40	7	0	Moderate	Immediate	3-5	—		No cyanosis produced at this reduced thialbarbitone dosage
Thialbarbitone i.v.	40								
5-15 min. after D.N.C. i.p.	20	4	25	Deep	"	10-23	1 hr.	++	
Thiopentone i.v.	10	8	0	Mild	Immediate	3-5	—		Immediate cyanosis and rapid death in 7/8 animals after barbiturate in D.N.C.-treated group. No cyanosis in survivor
D.N.C. i.p.	20	8	12	Deep	"	34	1½ hrs.		
Thiopentone i.v.	30								
5-10 min. after D.N.C. i.p.	20	8	88	Deep	Immediate	90 (1 survivor)	1-20 min.	++	
Thiopentone i.v.	30								
5-10 min. after D.N.C. i.p.	10	4	0	Deep	Immediate	25	—	—	Duration of narcosis similar to that in thiopentone control group at 30 mg./kg.
Thiopentone i.v.	10								
5-10 min. after D.N.C. i.p.	20	4	0	Mild to moderate	Immediate	10	—	+	

* Deep: Flaccid anaesthesia. Moderate: Inert, but muscle tone still present. Mild: Weakness, ataxia.

enough to cause characteristic signs of poisoning and profound disturbances of cellular oxidation-phosphorylation processes. Low D.N.C. dosage did not appear to potentiate high thiopentone dosage, whereas high D.N.C. dosage did appear to potentiate even quite low thiopentone dosage. The distribution of characteristic deaths due to D.N.C. was fairly equal in the D.N.C.-barbiturate and D.N.C. control groups, the implication being that, although high D.N.C. dosage potentiated the effects of all but one of the barbiturates tested, the barbiturates did not under these conditions potentiate or mitigate the toxicity of D.N.C.

We have been unable to find any instances in the published literature of severe D.N.C.-poisoning in humans being treated by sedation by barbiturate drugs, although in their report on a case of severe but non-fatal D.N.C.-intoxication Pollard and Filbee (1951) refer to sedation as part of the treatment adopted. During the past three years no cases of fatal or serious D.N.C.-poisoning have occurred in this country, so perhaps the therapeutic problem of D.N.C.-barbiturate synergism has not yet occurred in practice. It is worth noting, however, that D.N.P. itself still has some industrial use in the chemical and explosives industries, and that Brody and Bain also found that chlortetracycline ("aureomycin"), thyroxine, and methadone have considerable dissociating properties *in vitro*.

Summary

A series of experiments using rats has shown that in the presence of sufficiently high dosages of dinitro-*o*-cresol to cause characteristic D.N.C.-poisoning five of the six barbiturates tested were significantly potentiated in the rapidity of onset, depth, and duration of their narcotic effects.

The action of the two thiobarbiturates tested—thiopentone and thialbarbitone—was potentiated so that normally non-fatal anaesthetizing doses led to almost immediate cyanosis and death. Of the oxygen barbiturates, pentobarbitone, amylobarbitone, and phenobarbitone were markedly potentiated by D.N.C., but hexobarbitone did not appear to be significantly influenced.

Barbiturate potentiation by D.N.C. appeared to require the presence of high D.N.C. dosages. Low dosages, causing no obvious D.N.C.-poisoning, did not appear to increase barbiturate narcosis.

It is strongly recommended that barbiturate drugs, especially thiobarbiturates, should not be used for the induction of surgical anaesthesia in a person suffering from D.N.C.-poisoning, and that barbiturate sedation in such cases should be carried out with comparatively small dosages, in anticipation of a possibly enhanced effect due to the synergistic action of D.N.C. and the barbiturates on cellular respiration.

We are grateful to Dr. J. M. Barnes for drawing our attention to this subject, and for advice during the investigation.

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Blood donations to hospitals in England and Wales through the National Blood Transfusion Service in 1954 were more than ever before: 700,202, compared with 659,674 in 1953 and 669,000 in 1944, the year in which D Day fell. Last year 104,161 people gave their blood for the first time, and by the end of December the total strength of the donors' panel was 540,389, an increase of nearly 25,000 compared with 1953. To ensure that no one need be asked to give blood more than twice a year the National Blood Transfusion Service needs 650,000 regular donors.

Medical Memorandum

Thrombocytopenic Purpura during Chloramphenicol Therapy

Much has been written about the occurrence of blood dyscrasias during chloramphenicol therapy. Aplastic anaemia is the commonest finding, but agranulocytosis also occurs. Hodgkinson (1954) collected 31 cases of poisoning by chloramphenicol; 28 were cases of aplastic anaemia, while three had granulocytopenia with a normal erythrocyte count. He recommended that the maximum dosage of chloramphenicol administered to a child should be 100 mg. per kg. body weight daily for seven days.

Purpura has frequently been the first sign of a toxic reaction. In all reported cases such a purpura has been shown to be a manifestation of aplastic anaemia. Often the platelets have been greatly reduced: Wilson *et al.* (1952) recorded 9,000 platelets per c.mm., but such low figures have always been accompanied by a fall in both erythrocytes and granulocytes. A slight fall in platelets has been reported accompanying granulocytopenia without anaemia (Hodgkinson, 1954), but there seems to be no previous record of thrombocytopenic purpura as the sole manifestation of chloramphenicol poisoning.

CASE REPORT

A boy aged 5 was seen by his doctor on account of cough. A week after the onset of the disease whooping and vomiting began, and he coughed up a little blood. His doctor made a diagnosis of whooping-cough, and prescribed chloramphenicol palmitate, 60 minims (3.6 ml.) t.d.s. When he had received a total of 2 fl. oz. (57 ml.) of this (2 g. of chloramphenicol) he developed a widespread purpura. He was then admitted to Plaistow Hospital, a fortnight after the onset of his cough.

On admission there were ecchymoses on the limbs, trunk, palate, and alveoli, and inside the right cheek. He also had bilateral subconjunctival haemorrhages. The lungs showed no abnormal physical signs. There was a slight tachycardia, with occasional extrasystoles. The spleen and liver were not palpable. The temperature was 101.2° F. (38.4° C.). The haemoglobin was 95%. The white blood cells numbered 13,500 per c.mm. (32% polymorphs, 64% lymphocytes, and 4% monocytes). The platelets numbered 5,000 per c.mm., and the bleeding-time exceeded ten minutes.

Treatment with chloramphenicol was discontinued, and crystalline penicillin, 500,000 units, was injected eight-hourly. The platelets rapidly rose in number. On the day following admission there were 83,000 platelets per c.mm., and only a few fresh purpuric spots were found. On the 13th day after admission the platelets numbered 203,000 per c.mm., and the purpuric lesions had all healed. The cough also had disappeared. On the 20th day the platelets numbered 230,000 per c.mm. The liver and spleen were not palpable at any stage. The patient was then discharged, the white blood cells numbering 14,800 per c.mm. (40% polymorphs, 60% lymphocytes).

COMMENT

The interest of this case arises from two facts. Firstly, a severe but transient thrombocytopenia occurred during treatment with chloramphenicol, with no fall in the haemoglobin or granulocytes. Secondly, this toxic manifestation occurred after only 2 g. of chloramphenicol had been given to a child of 5 years, spread over five days. This is about a seventh of the maximum dosage recommended by Hodgkinson (1954).

My thanks are due to Dr. R. W. Tannahill, physician in infectious diseases to Plaistow Hospital, for permission to publish this case.

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