

ACUTE BARBITURATE POISONING

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One of the landmarks of twentieth century medicine and therapeutics was undoubtedly the synthesis of the first barbituric acid derivative with hypnotic properties. Barbitone, the di-ethyl ester of barbituric acid (malonyl urea) was first synthesized by Professor E. Fischer and Professor J. Mering in 1902. After a series of controlled tests on animals and humans, a year later, barbitone was exhibited on the market as Veronal, and was advertised widely as the panacea for all forms of insomnia and anxiety. Barely four years later, in 1906, the first fatality due to acute barbiturate poisoning following an overdosage of barbitone, was recorded.

AN EMERGENCY MEDICAL SYNDROME

During the last fifteen years the role of acute barbiturate poisoning in foreign centres as an emergency medical syndrome has come to the lime light and specialized, full-time, 'intensive care units' are equipped to deal with these emergencies as they arise.

A few representative figures will help to illustrate the state of affairs. In the United States of America, barbiturates account for 20% of cases of acute poisoning admitted to general hospitals — a figure in the region of 20,000 cases per annum. Despite a mortality rate of only 8%, in 1962 barbiturates took the toll of about 1,500 deaths. Besides this, barbiturate over-dosage accounts for 6% of all suicides, and 18% of all accidental deaths. In 1965 alone, 4,500 kilograms of barbiturates were sold in the United Kingdom and about 400 barbiturate deaths were reported. In the Scandinavian countries statistics provide fabulous figures: In Canada, A Richman and R. Orlaw have recently reported that deaths due to barbiturates have quadrupled from 63 in 1950, to 252 in 1963. Mortality was higher in females than in males and was highest in females aged 45-64.

In Malta there have been 57 admissions

for Acute Barbiturate poisoning over the last 5 years; of these 22 were male and 35 were females. 14 of the total number of patients were expatriates on holiday, or permanent residence in Malta. The age distribution of these cases is shown in the accompanying table.

Age	Male	Female	Total
Below 20	3	3	6
20-29	7	12	19
30-39	4	8	12
40-49	4	6	10
50-59	2	1	3
60-69	1	4	5
70-79	1	1	2
Total	22	25	57

CLASSIFICATION

Over fifty barbiturate derivatives have been retailed for clinical use. The following are the ones found with any frequency in cases of acute intoxication. Of the 'persistent' barbiturates i.e. barbiturates with a prolonged period of action Barbitone (Veronal), Barbitone Sodium (Medinal), and phenobarbitone (Luminal) are the commonest encountered. Of the medium-acting barbiturates, Butobarbitone (Soneryl), Amylobarbitone (Amatal), Pentobarbitone (Nembutal), Seco- or Quinal- barbitone (Seconal), and Aprobarbitone (Alurate) are the more commonly encountered. Barbiturate combinations are also common, such as Tuinal (Quinalbarb. Sod. & Amylobarb. Sod.) and Cabrital (Pentobarb. Sod. & Cabromal.). The ingestion of five to ten times the full hypnotic dose may give rise to quite heavy intoxication.

WHY?

The ingestion of large amounts of these drugs takes place either accidentally or with a suicidal intent. The accidental type of poisoning has been met with uncommonly in children who manage to have their fill of the capsules from the domestic medicine.

chest. Another form described by American authors as 'involuntary suicide' or 'automatism' has been described in regular partakers of these drugs who due to alcoholic intoxication or confusion from the ingestion of barbiturates themselves, manage to gulp down a second or perhaps a third helping of the drug in an attempt to doze off. The availability of barbiturates and the facility with which they may be procured has augmented, to a tremendous degree, the use of these drugs for suicidal purposes. This is particularly true in societies in which cultural level is high, competition keen, and instability rules. Such ingestions are often the acts of depressed patients or individuals with a psychopathic or hysterical personality who miscalculate the toxic dosage or who take them impulsively when inebriated. At times it is also a suicidal gesture performed in order to blackmail relatives or other associates. Thus it is not uncommon to have to deal with other drugs ingested by the patient in cases of acute barbiturate poisoning. Tranquillizers and antidepressants alcohol, aspirin, monoamine oxidase inhibitors and psycho-therapeutic drugs may find their way into the patient's stomach together with the barbiturates taken, complicating the clinical picture. Coal-gas poisoning may also be associated in suicidal cases.

RATIONALE OF TREATMENT

The prognosis of acute barbiturate poisoning has improved in the last decade owing to the greater efficiency and urgency with which the treatment is instituted. Clinically active treatment may be channeled along three ways namely:—

- a) the reduction of further absorption of the barbiturate,
- b) the abatement of the dangerous systemic effects of the barbiturate
- c) the enhancement of the rate at which the poison is removed from the body.

GASTRIC WASH-OUT

If the ingestion of the drug has been recent, gastric lavage may have its place both as a therapeutic as well as a diagnostic procedure. J.T. Wright of the London Hospital has proved by micro-chemical and chro-

matographic techniques that gastric wash-outs are of little value if more than two hours from the ingestion of the drug have elapsed.

According to Benseley and Joron the best method in which a gastric lavage may be performed in these cases is by pumping into the stomach via a Ryle's tube, dilute potassium permanganate until the aspirate starts turning pink. The remaining permanganate solution is then removed from the stomach, the mucosa is rinsed with water, and a tablet of sodium sulphate is left inside the stomach; otherwise 50 ml. of 50% magnesium sulphate are left inside the stomach.

Some scepticism is shown by the Scandinavian school of anaesthesia on the usefulness of gastric lavage. They postulate that the drugs often used in self-poisoning are the sodium salts of the respective barbituric acid derivatives, and, as such, are water soluble. So that if more water is introduced into the stomach a solution of the residual amounts of the undissolved barbiturates is made and some of it finds its way into the duodenum, thus further enhancing absorption. With gastric lavage there is also the increased risk of aspiration pneumonia: gastric juice and perhaps other infected secretions may find their way into the bronchi and pulmonary tissues. An attack of laryngospasm may also complicate the procedure, helping to aggravate the degree of anoxia in the unconscious patient. Peripheral vascular collapse is also known to have occurred during stomach wash-outs. In the series of 80 cases discussed by Fergusson & Grace all of which had undergone gastric lavage, five aspirated fluid during wash-out, 2 of whom developed apnoea and needed a tracheostomy; 2 others went into shock and vasopressors had to be used for resuscitation.

The conservative school of anaesthesia contends that gastric lavage always manages to rid the patient's stomach of a certain quantity of barbiturates. Sheelman and Shaw have shown that ingestion of large doses causes pylorospasm and thus a gastric wash-out is still very useful as most of the drug has been dammed back. Laryngospasm may be safe-guarded against by preliminary endotracheal intubation. Gastric la-

vage is still also of importance in cases when the stomach is ballooned with fluids or food.

If after a moderate overdose a patient is still fully conscious, R. Tattersall advocates the household remedy of induction of vomiting by digital stimulation of the fauces. However, in such cases the patient is also to be hospitalized for adequate observation and assessment.

CLINICAL PICTURE

Death is not instantaneous in acute barbiturate poisoning even though huge doses of the drugs may have been ingested. The absorption rate from the gastro-intestinal tract is not sufficiently rapid to provide massive doses to the brain and to the rest of the C.N.S. as to cause immediate obitus. However, a lowering of the level of consciousness is always present, usually associated with depression of respiration, possibly also with some degree of circulatory failure and cerebral damage.

The clinical picture is that of a patient who appears deeply asleep. The pupils react sluggishly to light, the deep tendon reflexes are diminished and plantar responses may be extensor. An erythematous papular rash may be associated. Respiratory failure develops in a couple of hours or after a longer period, depending on the type of barbiturate ingested.

MAINTENANCE OF RESPIRATION

On admission to hospital the patency of the airway is the first to be assessed. It is preferable to introduce a laryngoscope and thus to find out whether the laryngeal and the pharyngeal reflexes are present. If absent, a cuffed endotracheal tube is best inserted and any secretions present in the upper respiratory tract are aspirated. Respirations are to be maintained manually until an anaesthetist is available, at which time a positive-pressure respirator using an increased oxygen content is connected to the patient. The trachea and bronchi are to be aspirated frequently to maintain a clear airway. Hospitals with efficient, well-trained nursing staff prefer a tracheostomy and a cuffed tracheostomy tube, and constant attention to the airway. To facilitate drainage

from the respiratory tract the patient's bed is placed on shock blocks and the patient is turned frequently in bed.

Notwithstanding this the incidence of pulmonary atelectasis often followed by a fulminating broncho-pneumonia is still high. Thus prophylactic parenteral broad-spectrum antibiotics are to be given routinely, especially in centres where gastric lavage is performed.

THE USE OF ANALEPTICS

On the treatment of respiratory depression a great polemic exists between two schools of thought. The Scandinavian school championed by Nilsson calls for expectant treatment. The creed of the conservative school led by Koppanyi and Fagekas is the use of central analeptics as adjuvants to respiration.

Nilsson describes the clinical syndrome of acute barbiturate poisoning as, "an anaesthesia which is drawn out to last for days instead of lasting like a common so-called surgical anaesthesia for, at most, a few hours. Thus the rationale of this form of treatment is in accordance with anaestheiological principles. Faithful supporters of this form of therapy rely solely on a carefully planned, supportive, medical regime without the use of medullary stimulants. This expectant routine of treatment is accredited with low mortality rates ranging from 1.6% — 4%. This method entails two disadvantages. One cannot foresee when the patient will regain consciousness and when complications will set in. Secondly the patient provides a serious problem in a crowded, overtaxed general hospital and calls for the setting into operation of full-time 'intensive care units'.

Dobos et al in 141 cases followed over a period of seven years found no significant advantage of the use of analeptics over supportive therapy. Such complications of their use as cardiac arrhythmias, convulsions, and vomiting with subsequent fatal or intractable aspiration pneumonia, may even make things much worse.

The protagonists of the analeptic school insist on the fact that acute barbiturate intoxication is a definite indication for the use of central analeptics especially in severe

cases of intoxications and in cases due to poisoning by long-acting barbiturates. The search for the antidote to barbiturates has as yet been futile. Scores of drugs have been attributed with this property and the medical literature abounds with the clinical trials of these drugs in series of cases of acute intoxication. The mortality rates claimed by the various investigators range from 1.8% — 3.7%.

TYPES OF ANALEPTICS USED

Various analeptics have been used in the resuscitation of patients who have taken overdoses of barbiturates. Caffeine and Sodium benzoate, Leptazol and Nikethamide were some of the first drugs to be used. In long-acting barbiturate poisoning Pentylene tetrazol (Metrazol), Picrotoxin and Bemegride (Megimide) have been described as life-saving by F. Haler. In the cases of the medium-acting barbiturate poisoning Amphetamine Sulphate (Benzedrine) and Dexamphetamine Sulphate (Dexedrine) have been used. Balagot, Tsuji and Sadore from Chicago claimed that Bemegride is a direct antagonist to the barbiturates; no such effective antidotal effect has been demonstrated empirically. Ferguson and Grace tried to attribute the same property to Benzedrine in a series of 80 cases. In 1955 two new barbiturate antagonists were described: NP 13 i.e. Beta-Beta. Methyl. Ethyl. glutarimide which has a chemical structure definitely similar to the barbiturate ring system and D.A.P.T. i.e. 2:4 diamino 5. phenylthiazole hydrochloride or hydrobromide, itself a weak barbiturate antagonist, also a synergist of N P 13 and an excellent respiratory stimulant. In 1961 the American Silipo and his colleagues published the results of their clinical trials with Ethamivan i.e. Vanillic diethyl amide, discovered in Germany by Kratzl and Korasinha. R.J. Hoagland advocated the use of methyl phenidate (Ritalin).

The criterion in the use of these drugs lies with the side-effects that they are liable to produce. Bemegride is often regarded as the analeptic of choice on this account. 50mgm. of the drug dissolved in 10 ml. of N. Saline are injected every 5 minutes until the patient has regained consciousness. Overdosage is indicated by retching, vomiting, muscular twitchings and at times even

convulsions. These usually resolve if no further injections are administered but paradoxically thiopentone sodium (Pentothal) intravenously may become indicated. It is often combined with Nikethamide (Coramine, Nicamid); 2 to 8 ml. of a 25% aqueous solutions are injected i.v. This drug acts reflexly through the carotid chemoreceptors and directly on the medullary centres. Picrotoxin has also been used but is less favoured nowadays due to the convulsions that it may easily give rise to. It is given in doses of 6 mg. i. m. or 3 mgm. i. v. every fifteen minutes until the corneal reflex returns. Leptazol, also fallen into disuse, is now being revived by the American anaesthetists. 5 ml. of 10% Leptazol are given i.v. every 20 to 30 minutes. Amiphenazole hydrochloride (Daptazol) is another drug often used in combination with Bemegride; it possesses a direct stimulant effect on the C. N. S. with special reference to the respiratory centre. Before each Bemegride injection 1 ml. of a 1.5% aqueous solution is given intravenously. Amphetamine sulphate in these cases is given at the rate of 20 mgm. half hourly i.v. until the patient wakes up. Sheelman, Shaw et al. describe the use of a 0.5% (5 mgm./ml) of N P 13 and 1.5% (15 mgm./ml.) of D. A. P. T. in physiological saline. Convulsions may easily be brought about during this form of treatment. Ethamivan is given in doses of 400-500 mgm. i.v. start followed by continuous i.v. infusions containing 1.0 G. in 250 ml. of 5% dextrose in water. Side effects include generalized pruritus, muscular twitching, sneezing, excitation and restlessness. Probably the least dangerous and the least effective analeptic was the combination of caffeine and sodium benzoate; the time hallowed remedy of a strong coffee retention enema is well known.

The factor that is of great importance in the prevention of respiratory failure and cerebral anoxaemia, with consequent permanent damage to the brain, is oxygen. It is to be administered in all cases save those with only slight impairment of consciousness. If an endotracheal tube had been passed into the patient's larynx, oxygen is preferably administered through it. In all cases, meticulous care of the air-way by regular suction of secretions has to be instituted.

In 1951 Robie described the use of electrical stimulation through the head as a means of producing respiratory stimulation in barbiturate poisoning cases. He made use of a non-convulsive current and believed that this treatment significantly reduced the duration of coma. Blackly and Brookhart in '55 could not substantiate these findings in controlled experiments on dogs.

DEPRESSION OF VITAL CENTRES

Respiratory depression may be accompanied by depression of the near-by vasomotor and cardiac centres in the medulla with consequent peripheral vascular collapse and hypotension. Hershey and Zweifach even postulated a direct peripheral depressant effect on the myocardium and on the peripheral vascular system. In the treatment of this complication of barbiturate intoxication such first-aid measures as keeping the patient warm and raising the foot-end of the bed are not very effective on their own. The use of analeptics for respiratory depression may have some central effect on the vaso-motor centre. Such conditions are, however, best treated as cases of oligæmic shock with transfusion: glucose-saline, dextran and other 'plasma expanders', plasma, and even blood (R.C. Balgot, H. Tsuji, M.S. Sadore) have been used by different physicians. The role of vasopressors is, however, still debatable; some postulate a rebound phenomenon by which there is greater fall in blood pressure after the action of the vasopressor has withered away. Bensley and Joron have used noradrenaline acid tartrate (Levarterenol) in 5% glucose-saline, plasma or dextran. Ferguson used i.v. infusions of Neosynephrine and norepinephrine (Levarterenol) in glucose-saline. Methylamphetamine hydrochloride (Methedrine) has also been used.

An integral part of the treatment of such patients is a continuous and careful look-out for any changes in the state of the patient. These may be the index of deterioration of the cerebral damage. Scrupulous and regular recordings of temperature, pulse and respiratory rate, and Blood pressure are taken at least two-hourly. (According to de Bobo and Prescott this is to be done half-hourly.) Reflexes and a careful testing of the sensorium are to be recorded

at regular intervals as well as an estimation of the level of consciousness by the state of the pupils and by the response of the patient to stimulation.

FORCED DIURESIS

As barbiturates are weak organic acids, the urine by glomerular filtration and by secretion from the proximal convoluted tubules. In the non-ionised form they are diffusible and lipid soluble, and this permits back-diffusion from the renal tubular fluid into the peritubular blood, especially if the urine is scanty and acid (Weiner, Washington and Rindge).

The rate at which barbiturate is eliminated from the body is therefore enhanced by polyuria and alkalinity of the urine. This theory was first worked out by Koppányi in 1933. As early as 1945 De Bodo and Prescott had postulated an antidiuretic action of barbiturates. It was followed up by the work of Ohlsson in 1949 who proved this theory of 'blood lavage' by using mercurial diuretics and isotonic saline infusions. Giotti and Maynert have even shown that barbiturates are actually absorbed from the tubules, most probably through the proximal and to some extent from the distal tubules by a process of passive diffusion. Osmotic diuretics, as urea, have been found to interfere with this absorption perhaps due to an electrolyte imbalance which in turn blocks the passive barbiturate diffusion. Myschitsky and Lassen of Denmark, were the first to prove the effect of alkalinization and polyuria clinically by a controlled test on a series of 57 patients. They used two solutions: a 50% solution of urea in physiological saline and an electrolyte solution containing Sodium lactate, Sodium and Potassium Chloride and glucose. The latter solution was designed to alkalinize the urine and to prevent electrolyte depletion from the osmotic diuresis that would be produced by the urea solution. An i.v. infusion of 30 ml. of urea solution and 300 ml. of the electrolyte cocktail were given every hour for four hours. At the end of this period, the rate of the infusion was changed to the amount of urine that was being passed by the patient. A failure of a diuresis is indicative of acute tubular necrosis in which case haemodialysis is to be started immediately if the patient's

life is to be saved. In the series quoted only 3 of the patients died. The average duration of coma was definitely reduced by a third, and the complications of treatment were slight. There was no incidence of fluid retention but a few cases of electrolyte retracted under biochemical and electrocardiogram controls.

Other diuretics were tried. Cirksena and others tried solutions of mannitol with less spectacular results. In '61 the Americans R.C. Balgot, H. Tsuji and M.S. Sadore introduced a new osmotic diuretic, the tris-buffer THAM, trishydroxymethylaminomethane. A diuresis of 11 litres in the first 24 hours was produced during therapy and this lasted for 42 hours.

Other clinical trials were those of Laus in 1954 and of Waddell and Butler in 1957. These also have shown that the alkalosis that is induced by alkalization of the urine helps to lighten the depth of the barbiturate narcosis, especially in phenobarbitone poisonings.

Haemodialysis by the 'artificial kidney' has made it possible to save the life of a patient suffering from phenobarbitone or barbitone poisoning and patients having impaired renal function. This method is also most useful in the treatment of very severe cases of poisoning in those with normal renal function, as shown by Jorgensen and Wieth. The amount of barbiturate that can be recovered by haemodialysis in 7 hours is about that which can be obtained in 4½ days by diuresis. Not all barbiturates react to dialysis in the same way and this, according to Henry and Jackson, is due to the variability in the binding of the barbiturate molecule to tissue and plasma protein.

CONSTANT NURSING AND OBSERVATION

Part and parcel of the medical treatment of cases of acute barbiturate poisoning is the meticulous application of constant, painstaking, nursing care. Meticulous care of the patients' skin by constant turning in bed to prevent pressure sores, catheterisation of the bladder under aseptic conditions to prevent retention of urine with the possibility of infection and urolithiasis, and regular enemata to prevent distension of the patient's rectum are essential. The patient's

nutrition is kept up by i.v. drips of glucose at first and later, when the pharyngeal reflexes have returned, by tube feeding. Vitamin injections may also be necessary in neglected persons.

BULLOUS DERMATITIS

— A COMPLICATION

A recent accession to the syndrome of acute barbiturate intoxication is the description of the formation of bullae on the skin of such patients by G.W. Beveridge and A.A.H. Lawson. Definite dermal bullous lesions were noted in 19 (6.5%) out of 290 patients within 24 hours of the ingestion of the overdose. The lesions that appeared over pressure areas resembled a superficial burn and healed spontaneously without scarring unless secondary infection superceded.

THE NEED FOR THE PSYCHIATRIST

In cases of deliberate 'self-poisoning' by overdosage of barbiturates, the management following resuscitation is best achieved by psychiatric methods. Thus the *prima causa* of the patient's act is the factor that is to be carefully pondered into and discussed with him. The root of the trouble if possible is set right and hence is the importance of proper social welfare. Tranquillizers and other psychotherapeutic measures may have to be set into action on a long term policy to supplement the patient's mental attitude. As Neil Kessel, the Scottish psychiatrist, puts it 'the doctor is not to be impressed by the dozen tablets that the patient has taken but by the threescore that he can be prevented from swallowing'.

PREVENTION

The treatment and the prognosis of acute barbiturate intoxication have been greatly improved but as usual in medicine the preventive aspect is to be taken seriously too. Two alternatives remain to combat the rise in the incidence of barbiturate intoxication: either to stop using barbiturates or to safeguard their use. Various measures have been taken in different countries to control excessive prescription and use of barbiturates but these measures on their own have proved inadequate. Barbiturates

may be made less dangerous by combination with emetics and stimulants. Such preparations have been marketed, but they have not gone a long way in practice. Following the work on Bemegrade in 1954, its combination with barbiturates was tried. Trautner et al. (1957), and Gershan and Shaw (1957) were able to show that 10-20% of Bemegrade with barbiturates in capsule form reduced or even prevented the development of coma when doses up to 2.6G. of barbiturates were taken. Further proofs were the reports of Shunn in 1960 in which 50 'Phenaglate' capsules (Quinalbarb. 50 mg., Phenobarb. 25 mg. and Bemegrade 7.5 mg.) were taken with no resultant coma or respiratory depression and that of Heffer-

man (1959) who described two cases of ingestion of 24 capsules of 'Mylemide' (Amylobarb 100 mg. Bemegrade 10 mg.). This method has its limits too. B. W. Meynyn and K.J. Roberts have reported a fatality following the taking of 100 capsules of 'Phenaglate'.

Acute barbiturate poisoning has come to stay as a specialized, emergency, medical syndrome. Treatment of the more severe cases may require the co-operation of the experienced clinician, the anaesthetist to advise on the maintenance of an adequate airway and of assisted respiration, the biochemist and the chemical pathologist, and an expert nursing staff.