Section of Anæsthetics

President A C Forrester FFA RCS

Meeting February 2 1968

Gamma Hydroxybutyric Acid

Dr M D Vickers
(Royal Postgraduate Medical School, London)

Clinical Pharmacology and Current Status

The sodium salt of gamma hydroxybutyric acid (gamma-OH) was introduced into anæsthesia by Laborit *et al.* (1960) in France. It has been given to hundreds of thousands of patients in Europe and in the USA and will shortly be released in Britain. This paper summarizes the human pharmacology and current clinical status of this compound, presents some original observations and attempts to assess its potential place in British anæsthetic practice.

Chemistry and Biochemistry

Gamma-OH exists partly in the body as its internal ester gamma butyrolactone (*see* Fig 1). Both these substances have been identified in normal brain, as intermediate products in glucose metabolism (Bessman & Fishbein 1963, Fishbein & Bessman 1964). Of an injected dose of ^{14}C-labelled gamma-OH 80–90% appears as $^{14}CO_2$ in expired air, being broken down initially into 2-carbon fragments by beta-oxidation (Walkenstein *et al.* 1964). Coma is correlated with the brain concentration of gamma-OH (Roth & Giarman 1965). A simultaneous analysis of blood and CSF shows that coma is not correlated with CSF concentration (Fig 2). Laborit (1961) has suggested that excess of this substrate reorientates cellular metabolism, with a reduction of utilization of glucose-6-phosphate in the Embden-Mayerhoff pathway and an increase in utilization in the direct oxidative pathway or pentose shunt. Certainly the drug causes a shift of K^+ into cells and, in red cells, appropriate changes in metabolism can be demonstrated (Sonka & Sochorová 1967). Brain dopamine is also increased, probably due to an increase in decarboxylase activity (Boero *et al.* 1966), as is acetylcholine content (Beani *et al.* 1964).

However, the overall chemical composition of brains of animals sacrificed during gamma-OH coma barely differs from that found during barbiturate narcosis (Fleming & LaCourt 1965) although the regional distribution may vary. Furthermore, analysis of plasma and unwashed red cells for gamma-OH and gamma butyrolactone shows that there is virtually none in the cells. It is not clear, therefore, that the anæsthetic actions of this compound are due to alterations in metabolism, even though they can be demonstrated.

Clinical Effects

Central nervous system: Gamma-OH is a basal hypnotic whose primary action is on the cerebral

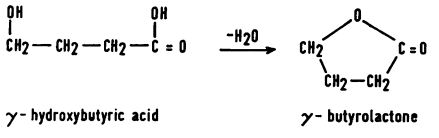

Fig 1 *Chemical structure of gamma-OH and its rearrangement as an internal ester*

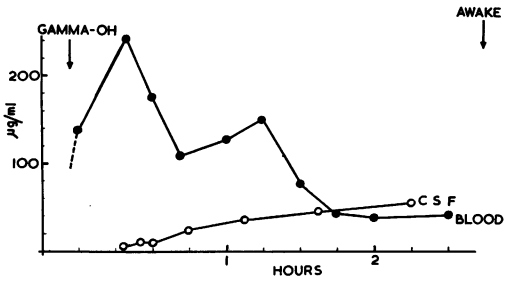

Fig 2 *Plasma and CSF concentrations of gamma-OH after single intravenous dose of 70 mg/kg*

Table 1
Femoral arterial carbon dioxide and oxygen tensions in patients having epidural analgesia followed by gamma-OH

	Immediately after onset of epidural analgesia	*5–10 min after 60 mg/kg gamma-OH*	*Mean change*
P_{ACO_2} (mmHg) (mean and SE of 8 patients)	37·7±0·8	39·9±0·6	+2·2 P<0·01
P_{AO_2} (mmHg) (mean and SE of 6 patients)	82·6±4·0	80·0±3·2	−2·5 P>0·1

cortex. After an intravenous injection of 60–70 mg/kg the patient becomes progressively more somnolent and, over a period of five to fifteen minutes, passes into an unrousable coma lasting one and a quarter to one and three-quarter hours, after which he awakens rapidly. Smaller doses produce no coma and the patient may either fall into a sleep from which he can be roused, or become agitated and hypomanic. Although the patient cannot be roused, reflex autonomic activity is not depressed and surgical stimuli cause tachycardia, hypertension, sweating and phonation. In conventional terms, it lacks any analgesic action.

This brisk responsiveness of brain stem centres can be correlated with a finding of a normal arterial carbon dioxide tension. Dr Steel and I have detected a small but statistically significant rise in arterial carbon dioxide tension and a comparable but statistically insignificant fall in oxygen tension in patients already analgesic from epidural blockade when given gamma-OH (*see* Table 1). These are comparable to the changes seen with the onset of sleep.

During induction with gamma-OH alone, random clonic movements are frequently seen. These are not associated with an epileptic discharge (Solway & Sadove 1965). The subjective symptoms may be disagreeable. Depression of the reticular formation of the brain stem with a small dose of barbiturate markedly hastens induction and abolishes the muscle movements; this is associated with a rise in blood level of gamma-OH (Helrich *et al.* 1964). Sedative phenothiazines also suppress the tendency to extrapyramidal movements.

The EEG is unique and there is marked species difference. In cats the behaviour and EEG are so bizarre that it can be questioned whether unconsciousness is present at all; the tracings are suggestive of epilepsy (Winters & Spooner 1965). In man there is no initial fast activity comparable with that seen with barbiturates but a steady development of slow, high voltage waves. Clinical arousal persists after EEG arousal has disappeared and at this stage amnesia is present. The disappearance of clinical arousal is accompanied by electrical silence punctuated by high-frequency bursts similar to K-complexes (Schneider *et al.* 1963). During light coma and emergence from deep coma there are periods of paradoxical sleep, with rapid eye movements and dreaming (Yanagida *et al.* 1965).

Vascular system: The blood pressure may rise about 10 mmHg or fall by a similar amount and there is a moderate bradycardia. This is accompanied by a moderate fall in cardiac output, which is reversed by atropine (Virtue *et al.* 1966). In lightly anæsthetized, curarized patients, the changes in arterial pressure and heart rate are accompanied by a rise in central venous pressure which partially persists even if the bradycardia is counteracted. The cardiovascular system retains its normal reactivity during gamma-OH coma and surgical stimuli cause tachycardia, hypertension and a rise in cardiac output. This response is blocked by drugs which depress the reticular-activating system, such as the phenothiazines. There are no ECG changes, apart from bradycardia, unless there is a pre-existing depletion of K^+. In animals gamma-OH protects against arrhythmias, whether induced by experimental infarcts, adrenaline or hypothermia, (Hernandez *et al.* 1966, Garcia *et al.* 1966). It doubles the survival time of anoxic rabbit hearts (Herold *et al.* 1961).

Other systems: Gamma-OH causes muscular hypotonia by depressing spinal internuncial neurones (Basil *et al.* 1964). There is an increase in the amplitude and frequency of uterine contractions during labour and the uterus becomes more sensitive to oxytocic drugs (Alfonsi & Massi 1964). It produces a cathartic release of emotion in some cases of anxiety (Du Couédic *et al.* 1964). There have been no reports of liver or kidney toxicity attributable to gamma-OH.

Potential Indications and Personal Experience

Gamma-OH by itself will provide sleep but will not protect against surgical stimuli. In all situations, apart from pre-medication and night sedation, it is essential either to provide protection with regional analgesia or to control autonomic reactivity with drugs such as phenothiazines. When used as an induction agent it is more satisfactory when combined with a small dose of a short-acting barbiturate. The following discussion assumes these generalizations.

To guarantee unconsciousness without toxicity: Its reported anti-arrhythmic and anti-anoxic potential makes gamma-OH particularly attractive for cardiopulmonary bypass, in which it will also ensure unconsciousness without toxicity or depression of vital centres. We have found it

particularly valuable in the post-operative management of such patients and others requiring artificial ventilation.

Obstetrics: It has been used in cases of incoordinate uterine action for normal delivery and in operative obstetrics. An assessment of the obstetric indications is not within the province of this paper. Gamma-OH is unlikely to achieve as great a popularity for normal delivery in the UK as in some continental centres (Alfonsi & Massi 1964), because of the relatively fewer number of normal deliveries conducted by doctors. It increases the incidence of forceps delivery. Dr Tunstall (1968*b*) reports on its use in operative obstetrics.

Endoscopies: Gamma-OH provides a continuing smooth narcosis which is extremely useful for prolonged laryngoscopies, bronchoscopies and bronchograms. It can be combined with topical analgesia and spontaneous ventilation or with relaxants and intermittent ventilation or diffusion oxygenation.

When air breathing is desired or necessary: Gamma-OH provides a less toxic alternative to the many cocktails which have been advocated for cardiac catheterization in children and its successful use has been reported (Bizot & Laborit 1965, Manni *et al.* 1964, Seebacher *et al.* 1966). I have used it on several occasions without encountering any special problems; angiography has also been done without a relaxant or controlled ventilation. Larger doses of gamma-OH (80–100 mg/kg) are usually necessary in children. Although there may be nothing active to do after the initial injection, the anæsthetist is not superfluous.

Where inhalational anæsthetic agents are not available, gamma-OH may also find a place.

Sleep-cover for operations under local anæsthesia: Dr Steel reports (1968) a series of patients operated on under epidural analgesia, asleep on gamma-OH and breathing air. Tunstall (1968*a*) has reported on its use in conjunction with infiltration analgesia for abdominal surgery.

It can be combined with the Bier technique of intravenous regional analgesia or any conventional regional technique. Although this may be more comfortable for the patient when an anæsthetist is not available, safety depends on judging the correct dose of gamma-OH: doses of gamma-OH should be reduced to 50–60 mg/kg when large quantities of analgesic may be absorbed systemically or coma will be unduly prolonged. Unless, however, there are particular reasons why nitrous oxide may not be given, it is difficult to see any reason why gamma-OH should replace it.

Neuroleptanalgesia: Similar arguments apply when potent analgesics are given in doses which necessitate controlled ventilation; there is little advantage in using gamma-OH and air instead of N_2O/O_2 mixture. Indeed, spectacular hypertension has been seen with this combination. Droperidol seems to be far less effective than phenothiazines in suppressing the reticular-activating system and large doses of systemic analgesics do not necessarily block the relevant reflexes. Gamma-OH has been combined with lesser degrees of neuroleptanalgesia for radiological examinations, such as air encephalography and arteriography when painful stimuli are absent or few (Memoli *et al.* 1964).

Premedication: Oral gamma-OH is an effective hypnotic and may find a place in the premedication of children. When given alone there is a tendency to vomit within the first hour after administration and if arousal takes place there is little residual drowsiness (Root 1965). Preliminary observations at the Hammersmith Hospital suggest that trimeprazine 2 mg/kg two hours preoperatively and gamma-OH 80 mg/kg one hour pre-operatively avoid both these difficulties and markedly increase the proportion of patients asleep at induction.

Intensive care: Its metabolic effects have been cited as indicating a place in the therapy of shock (Leterrier *et al.* 1963). Robinson *et al.* (1968) report some of these effects. At the Hammersmith Hospital it has proved to be of value in patients requiring artificial ventilation. The hypotonia is, no doubt, a useful adjunct to the relief of anxiety and accompanying somnolence but we have been surprised to find it much more effective than phenoperidine in getting patients to synchronize with the ventilator.

Gamma-OH is of great interest and will find application in certain restricted circumstances almost immediately. There are many facets of its behaviour which are still inadequately investigated and until they are it will not be possible to assess its more general applicability.

Acknowledgments: I am extremely grateful to Dr Violet Anderson, formerly of Glaxo Laboratories, for initially stimulating my interest in this compound and for advice and assistance; and to Glaxo Laboratories for the blood and CSF analyses of gamma-OH.

REFERENCES

Alfonsi P L & Massi G B (1964) *Ann. Anésth. franç.* 5, Suppl. Anésthésie en Obstétrique, 23

Basil B, Blair A M J N & Holmes S W (1964) *Brit. J. Pharmacol.* 22, 318

Beani L, Bolletti A & Bianchi C
(1964) *Acta anæsth.* (*Padova*) **15**, Suppl. 3, 89
Bessman S P & Fishbein W N (1963) *Nature* (*Lond.*) **200**, 1207
Bizot J & Laborit G (1965) *Agressologie* **6**, 223
Boero G C, Caboni F, Crabai F, Vargui L, Rudas N & Gessa G L
(1966) *Rass. med. sarda* **69**, 215
Couédic H du, Couédic A du & Voisse M (1964) *Agressologie* **5**, 73
Fishbein W N & Bessman S P (1964) *J. biol. Chem.* **239**, 357
Fleming M C & LaCourt S (1965) *Biochem. Pharmacol.* **14**, 1905
Garcia L, Pisanty J & Quijano R (1966) *Rev. mex. Anest.* **15**, 43
Helrich M, McAslan T C, Skolnik S & Bessman S P
(1964) *Anesthesiology* **25**, 771
Hernandez J A S, Bisteni A & Manzano S S
(1966) *Rev. mex. Anest.* **15**, 107
Herold M, Kabacoff C & Cahn J (1961) *Agressologie* **2**, 551
Laborit H (1961) *Agressologie* **2**, 439
Laborit H, Buchard F, Laborit G, Kind A & Weber B
(1960) *Agressologie* **1**, 549
Leterrier F, Baron G, Brue F, Delcambre J P & Laborit H
(1963) *Agressologie* **4**, 343
Manni C, Sarcelli L & Gennaioli D
(1964) *Acta anæsth.* (*Padova*) **15**, Suppl. 3, 53
Memoli G, Starita D & Mazzarella B
(1964) *Acta anæsth.* (*Padova*) **15**, Suppl. 3, 237
Robinson J S, Tomlin P J & Morris L
(1968) *Proc. roy. Soc. Med.* **61**, 824
Root B (1965) *Anesthesiology* **26**, 259
Roth R H & Giarman N J (1965) *Pharmacologist* **7**, 174
Schneider J, Thomalske G, Trautmann P & Thomalske G
(1963) *Agressologie* **4**, 55
Seebacher J, Ben-Ismail M, Lockhart A, Scebat L & Lenègre J
(1966) *Arch. Mal. Cœur* **59**, 1003
Solway J & Sadove M S (1965) *Anesth. Analg. Curr. Res.* **44**, 532
Sonka J & Sochorová M (1967) *Agressologie* **8**, 261
Steel G C (1968) *Proc. roy. Soc. Med.* **61**, 825
Tunstall M E
(1968*a*) *Brit. med. J.* i, 315
(1968*b*) *Proc. roy. Soc. Med.* **61**, 827
Virtue R W, Lund L O, Beckwitt H J & Vogel J H K
(1966) *Canad. Anæsth. Soc. J.* **13**, 119
Walkenstein S S, Wiser R, Gudmundsen C & Kimmel H
(1964) *Biochim. biophys. Acta* (*Amst.*) **86**, 640
Winters W D & Spooner C E
(1965) *Electroenceph. clin. Neurophysiol.* **18**, 287
Yanagida H, Tachibana N & Yamamura H
(1965) Int. Congr. physiol. Sci., Tokyo; abstract 1089

Professor John S Robinson,
Dr P J Tomlin and Miss L Morris
(*Queen Elizabeth Hospital, Birmingham*)

The Metabolic Responses following Gamma Hydroxybutyric Acid [*Abridged*]

Among the metabolic responses following anæsthesia and surgery which cannot be considered beneficial to the patient are the retention of sodium and chloride and the increase in catabolism with the consequent increased urinary loss of nitrogen and potassium. Gamma hydroxybutyrate (gamma-OH), given over a period of time, could modify post-operative catabolism and reduce the nitrogen and potassium losses after surgery, so it was decided to see if a single dose of gamma-OH, used as an intravenous induction agent, would have the same effect, and to investigate its hypokalæmic and hypoglycæmic action during anæsthesia.

Few reports of the drug's metabolic effects contain much controlled data; so we investigated the effects of gamma-OH under controlled conditions on fit patients undergoing simple routine surgery and compared it with the standard intravenous induction agent, thiopentone. The two drugs were investigated under as near identical conditions as possible; healthy volunteers who were unlikely to receive intravenous fluids during operation were studied, the operations being herniorrhaphy, varicose vein ligation and hæmorrhoidectomy. The patients were matched for sex, age, weight, operation, anæsthetic technique and operation time. There were 12 patients in all, forming six very closely matched pairs: anæsthesia was induced in each of the pairs with either 4 g gamma-OH or 200 mg thiopentone and maintained with either nitrous oxide and 1% halothane with spontaneous respiration for each of that pair, or nitrous oxide oxygen hyperventilation anæsthesia with curare relaxation. Thus the only difference in the anæsthetic management of each pair was the choice of the induction agent.

Pre-operative twenty-four-hour urine collections were made and two further collections were made over the next two post-operative days; from these the total nitrogen, potassium and sodium urinary excretion were determined. Before the induction of anæsthesia a venous blood sample was taken to determine the control values; after induction of anæsthesia arterial samples were withdrawn every fifteen minutes for the determination of electrolyte and acid base state. Thirty minutes after termination of anæsthesia and whilst the patient was breathing room air spontaneously, a further arterial sample was taken; on the two post-operative days capillary blood samples were taken for the determination of acid base state.

Per-operative Results

There was no difference between the effect of thiopentone and gamma-OH on the serum potassium, chloride and – after allowing for the sodium content of the induction drug – on the serum sodium. The blood urea rose slightly but equally in both groups of patients. There was no difference in the effect of thiopentone and gamma-OH on the cortisol response to surgery. The blood sugar rose by 25 mg/100 ml in the gamma-OH patients but only by 10 mg/100 ml in the thiopentone patients, and this difference between the two induction drugs was statistically significant. Blood gas results indicated that the alveolar/arterial oxygen gradient during anæsthesia was equal in the two groups of patients. Both sets of patients developed a slight metabolic alkalosis during anæsthesia, but this was more marked in those given gamma-OH and it persisted over the next two post-operative days.