

## Complications of baclofen overdosage

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### Summary

A 39-year-old female patient who had been receiving 30 mg of baclofen daily for 5 months was admitted to the hospital about 12 hr after an overdose of this drug (450 mg). On admission, she was comatose, flaccid, and in respiratory failure. Later she developed muscle twitchings and had several epileptic fits. She was treated symptomatically and became conscious within 36 hr. However, approximately 65 hr after the overdose she developed sinus tachycardia which was successfully treated with oral propranolol. Plasma concentrations, as measured on days 2 and 3, were within the therapeutic range but the elimination half-life was prolonged.

### Introduction

Baclofen is a derivative of a naturally occurring  $\gamma$ -aminobutyric acid (GABA) (Faigle and Keberle, 1972) and is used for the treatment of muscle spasticity (Paeslack, 1972). It exerts a long-lasting attenuating effect on muscle tone and, in the recommended therapeutic dosage, predominantly acts at the spinal level (Koella, 1972). Side effects are occasional and usually restricted to sedation, diarrhoea and confusional states (Paeslack, 1972). GABA is considered to be an inhibitory neurotransmitter and massive overdose with baclofen has been reported as being associated with impaired consciousness, respiratory depression, muscle weakness, involuntary jerking movements and epileptic convulsions (Paeslack, 1972; Paulson, 1976). A case is now reported of baclofen overdose who not only presented with the above features but also developed prolonged sinus tachycardia during the recovery phase.

### Case report

A 37-year-old female was admitted to the Intensive Care Unit following an overdose of approximately

45 baclofen tablets (450 mg) which had been taken about 8-10 hr previously. She had been prescribed this medication for muscle spasticity associated with basilar impression due to an arachnoid cyst of the posterior fossa about 5 months before this incident. On admission, she was comatose, hypotonic, and all reflexes were absent. Pupils were dilated and fixed but there was no evidence of papilloedema or pulmonary oedema. Her BP was 110/70 mmHg and a routine ECG was normal with a heart rate of 80/min. However, she had central cyanosis and her respiration was slow, irregular and shallow. She was ventilated and treated with various supportive measures, and had a satisfactory diuresis within 2 hr of being admitted.

Later she developed spontaneous muscle twitchings and had several epileptic fits (Table 1). Her level of consciousness improved slowly and she became fully conscious and was able to manage without ventilation approximately 36 hr after the overdose. During this period her BP and heart rate remained steady. However, she developed sinus tachycardia (150/min), 65 hr after the overdose, which was treated with oral propranolol with fairly good control of heart rate (100/min) within 24 hr. Her heart rate became steady (80/min) after 48 hr. There was no further complication. She was seen by a psychiatrist and thought to have been acutely depressed at the time of the overdose, but not during the recovery period.

### *Baclofen plasma concentrations*

It was not possible to monitor the plasma concentration of baclofen for the first 26 hr of being admitted because of the lack of facilities. However, on days 2 and 3, serial plasma samples were collected for baclofen concentration, stored at  $-20^{\circ}\text{C}$  and later estimated by a gas liquid chromatography method using an electron capture detector (Degen and Reiss, 1976). The results are shown in Table 1.

TABLE 1. Summary of the clinical state of a patient with baclofen overdose (9 mg/kg) and the plasma concentrations

Approx. time after overdose (hr)	Plasma level* (ng/ml)	Clinical state	Treatment and comment
8-10	-	Comatose and hypotonic respiratory depression	Artificial ventilation
12-26	-	Muscle twitchings, epileptic fits	Diazepam, i.v.
36-38	197	Conscious but drowsy	Off ventilator
40-42	159		
48-50	135	Conscious and alert	Therapeutic plasma levels
60-62	100		
65-67	129	Sinus tachycardia, HR, 150/min. BP, 130/80 mmHg.	Oral propranolol
80-84	-	HR 100/min.	-

\* Elimination half-life ( $T_{1/2}$ )=34.5 hr. HR=heart rate.

It will be seen that although the plasma concentration of baclofen at 36 hr was within the therapeutic range, the rate of fall was rather slow and there was a secondary peak. Plasma elimination half-life of baclofen in this patient was much longer (34.6 hr) than that observed following therapeutic dosage (40 mg/day, 3-4 hr) (Faigle and Keberle, 1972).

### Discussion

Baclofen crosses the blood brain barrier poorly (Faigle and Keberle, 1972), and in the recommended therapeutic dosage its central effect is almost negligible. However, massive overdosage is characterized by central depression as observed in this patient and reported previously (Paulson, 1976). Following oral administration, this drug is well absorbed and rapidly gets excreted through the kidneys. Hence, there is very little point in carrying out gastric lavage unless the patient is brought at a very early stage and attention should be paid to promote diuresis.

Animal experiments with radio-labelled baclofen indicate that concentrations in nerve tissue and brain are lower than in blood, but the apparent elimination rate in 24 hr from nerve tissue is much slower (Faigle and Keberle, 1972). This probably was partly responsible for the prolonged period of unconsciousness and other CNS complications following a massive overdose, even when the plasma concentrations of baclofen were within therapeutic range. In addition, the generous use of diazepam in these patients (Paulson, 1976; Ciba Labs, Horsham, personal communication, 1979), to control epileptic convulsions, probably contributed further to the duration of unconsciousness. Despite this drawback and in view of the associated severe respiratory depression, diazepam or clonazepam remain the treatment of choice to control epileptic convulsions. There was no evidence of increased salivation or increased cholinergic activity in this patient, as suggested by Paeslack (1972).

Plasma concentrations of baclofen in this patient, as estimated on days 2 and 3 were all within therapeutic range. It is difficult to explain the rise in baclofen concentration on the 3rd day which has also been observed by other investigators. This may have been due to a change in the volume of distribution of the drug, or to a significant amount of the drug being recycled via the entero-hepatic system. In this patient, elimination half-life (34.5 hr) appeared to be much longer than was observed in healthy subjects following a single oral dose (4 hr). It should be emphasized that this patient had already been receiving 30 mg of baclofen daily for 5 months and a further massive overdose may have resulted in a saturation of plasma protein and tissue-binding sites. Similarly, a longer half-life (65.5 hr) was observed in a patient who received amitriptyline for 52 weeks (Ghose, 1980), although this drug's half-life during steady state was reported to be 36-40 hr following 2 weeks' medication (Braithwaite and Widdop, 1971). Both amitriptyline and baclofen are lipophilic drugs and their subsequent release from the lipid stores are probably slow and may be related to the degree of saturation.

It is possible that baclofen interacts with biogenic amines in man, and a decrease in cardiac adrenaline and noradrenaline contents has been reported in animals (Paulson, 1976). Prolonged tachycardia during the recovery phase when the plasma concentration of baclofen was not at the toxic level, could be due to a sudden increase in sympathetic activity following a period of depression. A depressive disorder is considered to be related to deficiencies of biogenic amines at the neuronal sites and it is not very clear whether chronic baclofen therapy had any role in the present patient's taking an overdose, when her affective state appeared to have been fairly stable in the past.

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