Atropine treatment for baclofen overdose

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Summary
A healthy 17-year-old girl took a single large dose (420 mg) of baclofen. She was conscious on admission to hospital, but within 3-5 hr of overdose showed signs of marked cerebral, cardiac and respiratory depression, flaccidity and hypothermia. Eight hours after overdose, atropine administered i.v. produced a worthwhile increase in cardiac output, ventilation and temperature, lasting for about 90 min. This is of therapeutic and theoretical interest, and supports the view that baclofen leads to cholinergic dominance.

Introduction
Baclofen (Lioresal, Ciba) is used to relieve spasticity in patients with spinal cord lesions. It is the β-(p-chlorophenyl) derivative of the neurotransmitter γ-aminobutyric acid (GABA) (Faigle and Keberle, 1972), and reduces the tonic activity of spinal γ-motor-neurones, probably acting at a novel receptor site (Bowery et al., 1980). In therapeutic doses, spinal effects predominate, although drowsiness may occur (Jones and Lance, 1976); however, with increasing doses, central depression becomes increasingly marked. Those cases of overdose reported in the literature (Paeslack, 1972; Jones and Lance, 1976; Paulson, 1976; Lipscomb and Meredith, 1980; Ghose, Holmes and Matthewson, 1980) have all been characterized by unconsciousness. Four developed myoclonus or epilepsy during the later stages of unconsciousness, but all survived. All these patients had pre-existing neurological disease, and all had been receiving baclofen therapeutically. A case is described of baclofen overdose in a fit young adult, who took no other drugs, and who was admitted before the onset of unconsciousness.

Case report
A healthy 17-year-old girl was seen 90 min after swallowing 42.10-mg tablets (8 mg/kg) of baclofen prescribed for her grandfather. She was tearful and agitated, and able to struggle powerfully. After gastric lavage she was admitted to the ward, where diuresis was induced with frusemide (20 mg i.v., 4 hourly) and i.v. fluids. Over the next 2 hr she became flaccidly areflexic, and responsive only to pain; gag and pupillary light reflexes were preserved. She had a sinus bradycardia of 48/min, BP 100/60 mmHg and a rectal temperature of 35-7°C. Her respiration was shallow (tidal volume 275 ml) and her respiratory rate depressed (10/min). Initially, rewarming was attempted by wrapping the patient in a foil blanket. The stimulus of attempted endotracheal intubation led to temporarily improved ventilation, but even with repeated stimulation her condition declined. Eight hr after admission her rectal temperature was 34-2°C, heart rate 40/min, BP 90/50 mmHg, respiratory rate 11/min and tidal volume 400 ml. Atropine sulphate (600 µg) was given i.v. and after 15 min her heart rate had increased to 94/min and BP to 110/70 mmHg. Over the next 60 min rectal temperature rose to 35-4°C, tidal volume to 550 ml and respiratory rate to 15/min. Two hr later the BP, heart rate and respiratory rate began to fall, but not so much as to require further treatment. They subsequently improved in parallel with motor power, and 18 hr after admission she had recovered completely.

Discussion
In man, maximum blood levels of baclofen are reached 1-2 hr after an oral dose, and the elimination half-life is 2-4 hr (Faigle and Keberle, 1972). This accords well with the time course of deterioration and recovery in this case. It also explains why plasma baclofen concentrations measured more than 24 hr after overdose (Lipscomb and Meredith, 1980; Ghose et al., 1980) have been in the therapeutic range, even in patients who have had long-term baclofen treatment before overdose. The present patient became unconscious and showed hypoventilation, hypothermia, flaccidity, bradycardia and hypotension. The hypoventilation may in part have been due to reduced muscle activity, but the low respiratory rate with a relatively preserved tidal volume...
volume suggests a central mechanism; the hyperthermia may also have had some central component, although muscle flaccidity and cholinergically mediated sweating and bronchial hypersecretion (Paulson, 1976) are also of importance. The bradycardia and hypotension were marked in this patient, and accord well with evidence from animal experiments (Fehr and Bein, 1974) that baclofen in high doses leads to vagal dominance.

Atropine in therapeutic doses is known to have a paradoxically stimulant effect on the reticular activating system, similar to acetylcholine itself, probably by reducing feed-back inhibition (Kilbinger, 1978); and to stimulate respiration (Turner, 1969), although possibly not alveolar ventilation (Nunn and Bergman, 1964). It antagonizes the post-synaptic effect of acetylcholine in the autonomic nervous system. These effects of atropine should usefully counteract the vagal dominance induced by large doses of baclofen. The case of Ghose et al. (1980) was complicated by supraventricular tachycardia occurring about 5 days after the overdose. This might suggest that a drug prone to cause tachycardia would be contra-indicated. However, in the case of Ghose et al. there was no clear causal relationship, as the patient had therapeutic plasma concentrations of baclofen, had previously taken baclofen for 5 months, and had received other treatment. It may be of interest that Fehr and Bein (1972) demonstrated tachycardia and tachypnoea with moderate doses of baclofen in animals, although these gave way to respiratory and cardiac slowing with large doses. Thus, the fear of provoking supraventricular tachycardias should not prevent atropine being used, at least initially.

It is concluded that in this case, atropine appeared to increase ventilation, heart rate and blood pressure, and core temperature. Atropine should perhaps be considered along with forced diuresis before resorting to artificial ventilation in cases of baclofen overdose.

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References


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