Pathogenetic Aspects of Bromocarbamide Intoxication*

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Summary. In bromocarbamide intoxication in humans, as in rabbits, the predominant feature is the endothelial damage characterized by desquamation and vacuolisation, followed by interstitial oedema. Consumption coagulopathy, as observed in some cases of human bromocarbamide intoxication and also in our experimental model, can be prevented by anticoagulant therapy with heparin and also, as could be shown in rabbits, with aggregation-inhibiting agents. These findings strongly suggest that consumption coagulopathy is only a secondary phenomenon which develops in the course of primary endothelial damage. Similarities in the histological findings of endothelial damage between bromocarbamide intoxication in humans and in rabbits and the so-called "Adalin purpura", which can be observed after chronic use of bromocarbamide, are discussed.

Introduction

The course and therapy of acute severe bromocarbamide intoxication in patients has gained attention only recently, because of its characteristic feature (Benke, 1968; Emmrich, 1969; Gruska et al., 1970, 1971; Daniels et al., 1972; Hagedorn, 1974). Intoxicated individuals undergo a typical sequence of respiratory insufficiency and consumption coagulopathy. The pathological substrate constitutes diffuse microthrombosis and interstitial oedema of the lung (Mittermayer et al., 1972a).

Takeda (1911) and Kwan (1912) were the first to show that bromocarbamide in rabbits induces sleep in a 10-fold higher concentration (1 g/kg body weight) than in humans. To produce similar pathological findings in the lungs of rabbits as are described in intoxicated humans a 2- to 3-fold higher dose is required (Mittermayer et al., 1972b).

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The present experiments were aimed at the question whether therapy with an anticoagulant (heparin) or inhibition of platelet aggregation will change the clinical course and pathological characteristics of bromocarbamide intoxicated animals. The purpose was thus to draw conclusions as to the pathogenesis of acute bromocarbamide intoxication and possibly also to the haemorrhagic phenomenon in chronic use of bromocarbamide.

Materials and Methods

Rabbits of both sexes weighing between 1.2 and 3.0 kg were intoxicated with 2.5 g/kg body weight bromocarbamide (bromisovalerianyl carbamide, Bromural®) suspended in 1% tylose gel administered through a stomach tube. During the experimental procedure the rabbits were protected against hypothermia. The animals were divided into three groups:

Group I (n = 8): control group intoxicated with bromocarbamide.

Group II (n = 5): bromocarbamide intoxication as in group I, but in addition heparin was administered in a dosage sufficient to raise the plasma thrombin time to above 1 min.

Group III (n = 7): bromocarbamide intoxication as above with, in addition, 2 mg/kg body weight of an aggregation inhibiting agent [Persantin derivate, 2.6-Bis (diethanolamino)-4-piperidino-pyrimido pyrimidine (Thomae/Germany)] injected intravenously before and 1 and 3 hrs after intoxication.

In all the rabbits platelets were counted before and 1, 3, 4 and 5 hrs after intoxication.

In addition to these experiments, platelet function tests were also carried out: 1. Spontaneous platelet aggregation was measured in a plasma platelet suspension (150000/mm³) 3 hrs after bromocarbamide intoxication by rotating the platelet suspension for 10 min and recording the change in optical density. As control, in the same rabbits, aggregation was measured 48 hrs before intoxication. 2. Aggregation on collagen was measured in a plasma platelet suspension (150000/mm³), according to the method of Heinrich and Roka (1970), at a constant temperature of 25°C. The change in optical density was recorded. As control, the same experiment was carried out 48 hrs before intoxication, in the same rabbits. These results were compared with those obtained 3 hrs after intoxication. A 120 μg dose of a commercial collagen (Horm/Germany) was used in these experiments.

Necropsy was performed on animals which died spontaneously, and specimens of 6 different organs were removed in all cases. After fixation in pH 7 buffered formalin the specimens were cut into 10 μg thick sections from the paraffine blocks. The samples were stained with haematoxylin-eosin, the PAS-reaction, Elastica-van Gieson and Goldner trichrome procedure.

For electronmicroscopic observation, skin from the lower abdomen, together with subcutaneous tissue, was fixed in 1% glutaraldehyde followed by 1% osmium tetroxide. After dehydration in an ethyl alcohol series, the material was embedded in Epon 812. Thin sections were stained with uranyl acetate and lead citrate.

Results

In group I we found a significant decrease in the number of platelets 1—4 hrs after the application of bromocarbamide, as compared with the values obtained before intoxication. This decrease in the number of platelets was significantly inhibited by the application of heparin (P < 0.01) and to the same degree by therapy with an aggregation inhibiting agent (P < 0.01) (Fig. 1).

The platelet function tests showed that there was no spontaneously increased formation of platelet aggregation after bromocarbamide intoxication. The tangent of the continuously registered extinction curve, after addition of collagen, was measured as the parameter of the collagen-induced aggregation. The mean values of the tangents in the control group, before intoxication, were 111.5° (±9) and 110.8° (±7) in the intoxicated group.