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## Glypentide: A new hypoglycaemic agent

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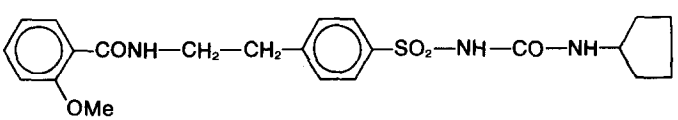
GLYPENTIDE is a new oral hypoglycaemic agent, known by the research code name UR-661.[1,2] Its chemical structure is *N*-[4-beta-(*o*-anisamidethyl)-benzenesulphonyl]-*N'*-cyclopentylcarbamide:




The activity and toxicity of glypentide was studied in rabbits, dogs and man.

Albino rabbits (1·5–2·0 kg) and beagle dogs (10–12 kg) were used. Glypentide was administered either by gastric intubation as a suspension in carboxymethylcellulose (0·5% w/v), in doses from 0·01 to 10 mg/kg body wt, or intravenously as a solution in distilled water at doses from 0·02 to 0·25 mg/kg. Control animals received an equal volume of the vehicle.

The animals were fasted overnight, water being allowed *ad lib.* Blood was collected from the vein (rabbits: ear marginal; dogs: saphenous) before and at various intervals after the administration of glypentide. Blood sugar was estimated according to the *o*-toluidine method.*

Glypentide lowered the blood sugar in albino rabbits and dogs (Figs. 1 and 2). In the rabbit, the maximum hypoglycaemic action was reached 4–5 hr after oral, and 3–4 hr after intravenous administration of glypentide. Twenty-four hours after the administration, the blood sugar levels had returned to normal. In all cases there was a dose–response relationship. In the dog, a single oral dose of 0·05 mg/kg glypentide reduced the mean blood sugar level by 11 per cent, 5 hr after administration. Higher doses induced greater hypoglycaemic responses, giving a dose–response relationship. Oral doses of 2 mg/kg, or higher, produced hypoglycaemic effects that lasted more than 24 hr.

According to these data, glypentide is approximately 1000 times more potent than tolbutamide in rabbits and 200 times more potent in dogs.[3]

Administration of a single oral dose of 5 mg glypentide to twelve healthy human subjects resulted in an intense and prolonged decrease of blood sugar levels. The maximum decrease (to 47 per cent of the control) was obtained two hours after administration and lasted 16 to 18 hr.[4]

* Merkotest Art. 3353.

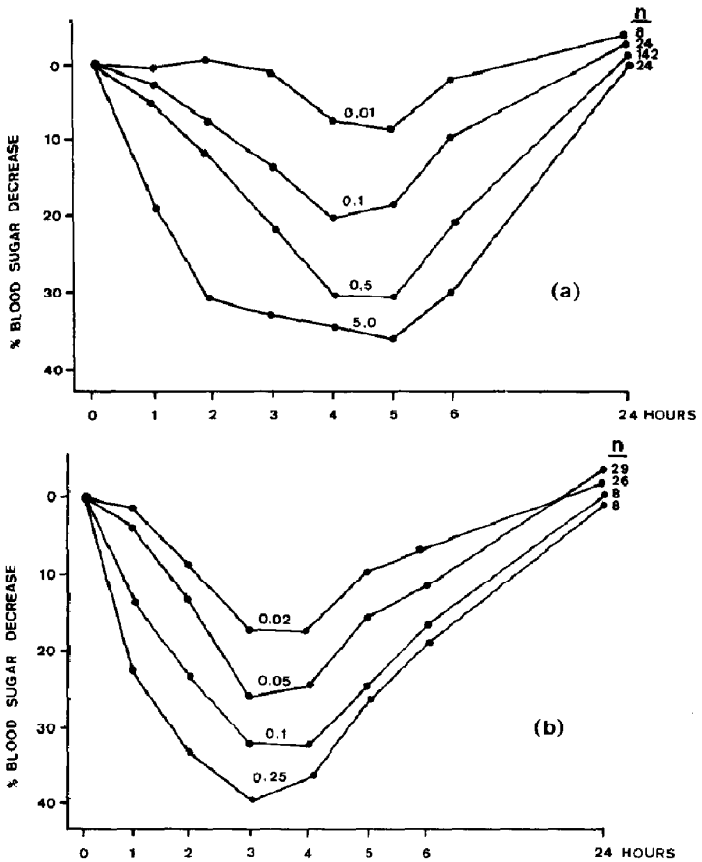



FIG. 1. Effect of Glypentide on blood sugar levels of fasted rabbits after oral (a) or intravenous (b) administration of different doses (mg/kg). Each point represents the mean value obtained with (n) animals.

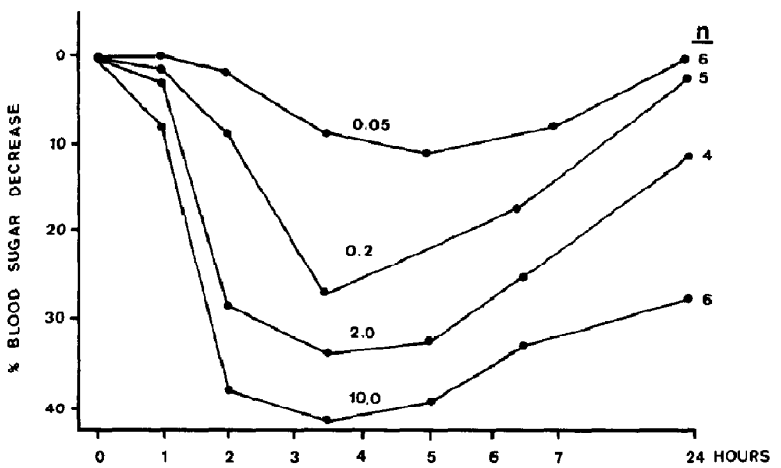



FIG. 2. Effect of Glypentide on blood sugar levels of fasted beagle dogs after oral administration of different doses (mg/kg). Each point represents the mean value obtained with (n) animals.

Studies on animals suggest that glypentide has the same mechanism of action as other sulphonylureas. In fact, 30 min after i.v. administration (jugular vein) of a single dose of 0·1 mg/kg glypentide to anesthetized rats (Nembutal®, 40 mg/kg), the mean blood sugar level was decreased by 28 per cent. The plasma insulin levels increased, reaching a maximum of 280 per cent (from 15 to 42 μU IMI/ml), 10 min after the administration.[5]

Glypentide stimulates insulin release from perfused isolated rat pancreas. The experiments were carried out according to the method of Sussman and Grodsky, modified by Fussgänger *et al.*[6] Glypentide was perfused at a rate of 60 μg/min in the presence of 5·5 mM glucose. Under these conditions insulin output increased from 210 to 563 μU IMI/min.[5]

A single oral dose of 15 g/kg of glypentide did not give rise to any toxic effects in rats, mice and guinea pigs. The oral $LD_{50}$ for rabbits and dogs exceeds 10 g/kg. Daily oral doses up to 400 mg/kg to rats for six months did not produce abnormal changes in the general condition, food consumption, hematological values, urine analysis and liver enzyme activity; at necropsy, no gross organ changes were observed and no abnormalitites were found microscopically. Similarly, daily oral doses up to 200 mg/kg to beagle dogs for 12 months did not produce any toxic manifestation.

Only a very small percentage of the animals treated with the highest doses of glypentide showed hypoglycaemic convulsions, which disappeared spontaneously. These very low toxicity values are similar to those of structuraly related hypoglycaemic sulphoylureas.[7–13]

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