CASE REPORT

Prolonged elimination of tolbutamide in a premature newborn with hyperinsulinaemic hypoglycaemia

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Abstract

So far, gestational diabetes treated with tolbutamide has never been associated with severe hypoglycaemia in the newborn when the mother's diabetes was well controlled. We report a case of a premature neonate, gestational age 34 weeks, with severe and long-standing hypoglycaemia from birth. The mother had well-controlled gestational diabetes, treated with tolbutamide from the 24th week of gestation until delivery. The neonate had inappropriately high levels of serum proinsulin, insulin and C-peptide relative to blood glucose concentrations. From day 19 after birth, the levels were normalized. Serum tolbutamide was 140.6 $\mu\text{mol/l}$ (38 $\mu\text{g/ml}$) at 3 h after birth. Zero-order kinetics were seen during the first 90 postnatal hours. The half-life of serum tolbutamide decreased from 46 to 6 h. It is suggested that tolbutamide, when given to the mother until delivery, may cause severe and prolonged hyperinsulinaemic hypoglycaemia in premature neonates. The initially prolonged tolbutamide half-lives and zero-order kinetics suggest immaturity of hepatic elimination during the first 2 days of postnatal life.

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Introduction

Sulphonylureas are rarely used in the treatment of gestational diabetes because of reports of neonatal hypoglycaemia and a presumed, but not documented, human teratogenic effect (1–3). In most reports, however, maternal intake of sulphonylureas until delivery has not been associated with neonatal hypoglycaemia, and this has never been reported for tolbutamide except for cases in which maternal glucose control was not described (4, 5).

Tolbutamide readily crosses the placenta by passive diffusion (6). More than 98% of serum tolbutamide is bound to serum proteins, especially albumin (7). The drug binds to sulphonylurea receptors on the beta cell surface. Sulphonylurea receptor activation, like mutations of the receptor, result in closure of potassium channels, depolarization of the cell membrane, calcium influx, and thence exocytosis of insulin (8, 9). Tolbutamide also stimulates pancreatic D-cell release of somatostatin (10). Somatostatin inhibits the sulphonylurea receptor. Tolbutamide may therefore limit its own insulin-secreting effect by stimulating the release of somatostatin. The drug is eliminated by hepatic microsomal oxidation, catalysed by the cytochrome P450–2C9 isozyme (11). In adults, the elimination is a first-order process with a marked interindividual difference (12). The half-life is usually 4–8 h.

We report a case of long-standing and severe hypoglycaemia with evidence of hyperinsulinaemia in a neonate of a mother treated with tolbutamide. Prolonged tolbutamide elimination was found.

Methods

Serum C-peptide, proinsulin and insulin concentrations were determined by routine DELFIA analysis (two-site two-step time-resolved immunofluorometric assay) (13) at the Department of Clinical Biochemistry, Odense University Hospital.

Serum tolbutamide was determined by an HPLC method (14), measuring the total of the unbound and protein-bound fractions.

A Medline search from 1/1966 to 12/1996 using the two search strategies [hyperinsulin* or hypoglyc*] and neonat*, and [tolbutamide or sulphonylurea or sulfonylurea] and neonat* was performed. Relevant referred articles before 1966 were found. The manufacturer Hoechst kindly made a search on tolbutamide in their own database and Micromedex from 1974 to 1996.

Case report

A male infant was born to a 37-year-old gravidaz para 2 with gestational diabetes. The mother had a 6-year

Figure 1 Series of simultaneous determinations of serum C-peptide (130–760 pmol/l), proinsulin (2–23 pmol/l) and insulin (12–77 pmol/l) relative to blood glucose. Grey areas on the figure and values in parentheses in this legend represent the unstimulated normal range in adults.

record of essential hypertension treated with an α - and β -blocker (labetalol, 600 mg/day). Because she had had gestational diabetes in her first pregnancy, she performed self-monitoring of blood glucose four times a day from the sixth week of gestation. At 11 weeks of gestation, the oral glucose tolerance test (OGTT) was abnormal. The diabetes was initially treated by diet. From 23 weeks of gestation, tolbutamide at a daily dose of 500 mg was added because of an increase in preprandial blood glucose to 9.5 mmol/l, assessed by self-monitoring. The tolbutamide dose was gradually increased to a maximum of 1500 mg from week 29. Glucose was well controlled, with no preprandial or bed-time blood glucose results above 9.7 mmol/l. Glycosylated haemoglobin (HbA_{1c}) values ranged from 5.0 to 5.8% in six samples from 6 to 34 weeks.

The mother had a prepregnancy weight of only 43 kg, height 157 cm and body mass index 17.4 kg/m². Weight gain and blood pressure were normal throughout pregnancy.

At 34 weeks and 4 days of gestation, the mother felt no intrauterine movements. Prior to, and after admission to hospital, blood glucose was 8.6 and 6.7 mmol/l respectively. Cardiotocography showed a flaccid curve. Emergency cesarian section was performed.

The Apgar score was 7/1, 8/5 and 9/10. Birth weight was 3200 g and birth length 49 cm, both values above 1 S.D. of the mean for gestational age. The baby had the appearance of mild diabetic fetopathy. Blood glucose 1 h after birth was only 0.8 mmol/l. A urine test showed no ketone bodies.

The child immediately received an intravenous bolus of 10 ml 20% glucose, followed by continuous

administration of 20% glucose (8 ml/h; 36.7 mg glucose/min per kg). At 3 h after birth, blood glucose was 1.3 mmol/l; it reached a minimum of 0.7 mmol/l twice within the first 4 h. From 10 h after birth, subcutaneous administration of the long-acting somatostatin derivative octreotide 18.75 μ g/kg per day (in four doses) was added, increasing to a maximum of 22.5 μ g/kg per day (in six doses) from day 2 to day 5 after birth, followed by a gradual reduction in dose.

Intravenous glucose was discontinued 3 days after birth; octreotide was discontinued 9 days after birth. The child was breastfed from day 7 after birth, 1 day after discontinuation of tolbutamide intake by the mother.

There were no signs of hypoxic–ischaemic encephalopathy.

Values for blood glucose, serum C-peptide, proinsulin and insulin at 3 h, 14 h, 61 h, 19 days and 83 days after birth are shown in Fig. 1 and Table 1. The first three samples were drawn during intravenous glucose infusion. Inappropriately high levels of C-peptide, proinsulin and insulin were recorded relative to the low blood glucose values. The samples taken on days 19 and 83 after birth showed unstimulated preprandial levels, which were all normal.

Two OGTTs (1.75 g glucose/kg) were performed (Table 1). At the first 61 h after birth, octreotide (22.5 mg/kg per day) was maintained. From high basal values, a pronounced response of proinsulin, C-peptide and insulin was seen. The blood glucose response was delayed, with a maximum of 11.1 mmol/l at 2 h. At 19 days after birth, the basal values and the OGTT blood glucose response were normal.

Table 1 Concentrations of blood glucose and serum C-peptide, proinsulin and insulin at 3, 14 and 61 h and 19 and 83 days after birth and 0, 60 or 120 min after OGTT.

Time after birth	Medication		Concentration		
			0	60 min	120 min
3 h	i.v. glucose and octreotide	Serum C-peptide	2077		
		Serum proinsulin	108		
		Serum insulin	340		
		Blood glucose	1.3		
14 h	i.v. glucose and octreotide	Serum C-peptide	5345		
		Serum proinsulin	64		
		Serum insulin	—		
		Blood glucose	2.9		
61 h	Octreotide	Serum C-peptide	1557	2177	3448
		Serum proinsulin	25	30	43
		Serum insulin	55	330	596
		Blood glucose	4.4	5.9	11.1
19 days	Nil	Serum C-peptide	636	3210	1736
		Serum proinsulin	7	10	10
		Serum insulin	—	—	—
		Blood glucose	4.1	12.4	3.7
83 days	Nil	Serum C-peptide	594		
		Serum proinsulin	8		
		Serum insulin	—		
		Blood glucose	5.0		

Values for serum C-peptide, proinsulin and insulin are expressed in pmol/l and those for blood glucose in mmol/l.

Serum tolbutamide concentration decreased from 140.6 $\mu\text{mol/l}$ (38 $\mu\text{g/ml}$) at 3 h after birth to 7.4 $\mu\text{mol/l}$ (2 $\mu\text{g/ml}$) at 90 h after birth. In a double arithmetic plot of serum tolbutamide concentration against time, the decline in serum tolbutamide showed an arithmetically linear regression (Pearson's correlation constant $r = -0.989$, 95% confidence interval -0.887 to -0.999), indicating zero-order kinetics. The first half-life was estimated to be 46 h, the second was 23 h, the third 11.5 h and the fourth, at 78–84 h after birth, was 6 h.

At 3 months of age, the child displayed normal psychomotor development. There was no history of cerebral convulsions or hypoglycaemia.

Discussion

Hyperglycaemia in poorly controlled gestational diabetes results in intrauterine hyperinsulinaemia, macrosomia and transient hyperinsulinaemic hypoglycaemia after birth (15). When gestational diabetes is well controlled, neonatal macrosomia and elevated umbilical cord serum C-peptide may still occur, but severe hypoglycaemia is not observed (16, 17), or is very rare.

In our case, the neonate was unexpectedly large for gestational age and the weight and height of the mother. The hypoglycaemia was more severe and long-standing than expected from the well-controlled gestational diabetes itself (HbA_{1c} 5.0–5.8%). This led us to evaluate the role of tolbutamide. For the first time, simultaneous

determinations of serum tolbutamide, C-peptide, proinsulin and insulin were performed in a neonate.

The diagnostic criteria of hyperinsulinaemic hypoglycaemia were fulfilled, with a glucose demand of well over 15 mg/min per kg to maintain a normal blood glucose level, and inappropriately high levels of serum C-peptide, proinsulin and insulin relative to blood glucose (18).

The concentration of tolbutamide could not be related to any toxic limit reported. There is no reported therapeutic level of serum tolbutamide for any age group, and the presence of serum tolbutamide in premature neonates has never been described.

In an experimental study by Miller *et al.* (4), maternal tolbutamide ingestion (500 mg or more) had little, if any, effect on the blood glucose of the term neonates. At 3 h after birth, serum tolbutamide concentrations of the neonates ranged from 10 to 54 $\mu\text{g/ml}$ (37–200 $\mu\text{mol/l}$).

The 3 h value of serum tolbutamide (140.6 $\mu\text{mol/l}$) in our patient was within that range, suggesting that tolbutamide had an enhancing effect on the sulphonylurea receptor in the premature infant. It may be speculated that the enhancing effect was caused by somatostatin deficiency or other endogenous factors related to prematurity.

Repeated measurements of tolbutamide clearly demonstrated acceleration of the elimination rate of tolbutamide with time, from the first very prolonged half-life of 46 h to the fourth half-life of 6 h within the normal adult range. The elimination showed zero-order kinetics, which has never previously been

reported for tolbutamide or for other sulphonylureas in premature or term neonates.

In one healthy term neonate experimentally exposed to tolbutamide 22 h after birth, the half-life was 24.4 h during the first 10 h, decreasing to 16 h during the following hours (19). As in our premature patient, prolonged tolbutamide elimination was found during the first 2 days of postnatal life only.

It is suggested that the availability of the eliminating isoenzyme cytochrome P450-2C9 is reduced in premature and term neonates during the first 2 days after birth. Postnatal factors, in addition to gestational age, may play a role in the maturation of the microsomal availability of cytochrome P450-2C9.

Transfer of labetalol across the placenta may aggravate hypoglycaemia in neonates by blocking the adrenergic response. In our case, labetalol was probably of little importance compared with the pronounced hyperinsulinaemia.

We conclude that the prolonged and severe hyperinsulinaemic hypoglycaemia may have been caused by a high tolbutamide level for a premature neonate combined with prolonged elimination of tolbutamide. The effect of tolbutamide on insulin secretion may have been enhanced by endogenous factors affecting the sulphonylurea receptor. Zero-order elimination was found in the first 90 h of life.

One of the purposes of improving maternal diabetic control in pregnancy is to minimise the degree of hyperinsulinism in the fetus. Although normalizing the mother's blood glucose levels, the use of tolbutamide in our premature patient appeared to promote hyperinsulinism instead of preventing it. It is suggested that the use of tolbutamide in gestational diabetes is counterproductive in the case of an unexpected premature delivery.

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