

1.1. Norfloxacin and hypoglycaemia

Introduction

Norfloxacin is a fluoroquinolone antibiotic. It inhibits bacterial deoxyribonucleic acid synthesis and can therefore be used as a wide spectrum antibiotic. Norfloxacin is registered for therapeutic use in *acute recurrent urinary tract infections, prostatitis, bacterial gastroenteritis, gonorrhoeic urethritis, proctitis and cervicitis* as well for *prophylactic use in neutropenic patients* [1-5].

Norfloxacin has been used internationally since 1983. Fluoroquinolones have both hypoglycemic and hyperglycemic effects in diabetic as well as non-diabetic patients [7]. Although a class effect is suspected, some fluoroquinolones have a more profound effect on glucose homeostasis, for example gatifloxacin [7-9] and temafloxacin [8], which were withdrawn due to this effect.

Levofloxacin is also believed to have hypoglycemic effects [9]. Evidence of ciprofloxacin effects on hypoglycemia is sparser and only based on case reports in patients using sulfonylurea in a pre-existing diabetes mellitus [8]. Hypoglycaemia is not mentioned in the SmPCs of norfloxacin [1-5]

Hypoglycaemia not related to diabetes treatment, salicylate intoxication or use of alcohol occurs seldom. Besides endogenous hyperinsulinism or rare malignancies or paraneoplastic effects, sepsis or starvation may induce hypoglycaemia [10].

Five cases of norfloxacin and hypoglycemia associated with norfloxacin use, including two cases of hypoglycaemia in non-diabetic subjects, are presented in this report.

Reports

On July 7, 2010 the database of the Netherlands Pharmacovigilance Centre Lareb contained five reports (Table 1) concerning hypoglycemia associated with norfloxacin use.

Table 1. Reports of hypoglycemia associated with the use of norfloxacin.

Patient, Number, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug Outcome
A 21494 F, 21 – 30 years	norfloxacin urinary tract infection	OAC (Mercilon®), ibuprofen	hypoglycaemia (2.9 mmol/l, postprandial 3.3 mmol/l)	two days; withdrawn; recovered glucose 4.4 mmol/l and 5.9 mmol/l prior hypoglycaemia during earlier norfloxacin treatment
B, 104591 F, 70 years and older	norfloxacin 400mg bd urinary tract infection	betahistine estriol ibuprofen magnesium hydroxide, paracetamol, haloperidole, rosuvastatin, omeprazole, rivastigmine	hypoglycaemia	three days withdrawn, glucagon therapy, recovered
C 73853 M, 31 – 40 years	norfloxacin 400mg urinary tract infection insulin diabetes mellitus type 1	not reported	hypoglycaemia glucose blood levels were not specified, however 20 units reduction of daily insulin need	one day; norfloxacin withdrawn; recovered

Patient, Number, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug Outcome
D, 75154 F, 61 – 70 years	norfloxacin 400mg cystitis metformin 1000mg bd insulin (lispro and glargin)	ipratropium salbutamole salmeterole/fluticasone montelukast prednisolone	hypoglycaemia (2.7mmol/l)	one day, withdrawn, outcome unclear due to unstable diabetes and infections unresponsive to antibiotic treatment, weeks later patient died due to non-related cause (cerebrovascular accident)
E 21415 F, 61 – 70 years	norfloxacin urinary tract infection 400mg daily glimpiride type 2 diabetes mellitus 3mg	metoprolol, valsartan, hydrochlorothiazide, triarterene, pravastatin	hypoglycaemia (2.9 mmol/l)	75 minutes discontinued, replaced by nitrofurantoin recovered despite ongoing glimpiride use

Lareb received five reports of norfloxacin associated hypoglycaemia, all reported by health care professionals and objectified by glucose levels or need of insulin, or given the administration of glucagon in patient B, most probably objectified. In all five cases the reported reaction consisted of both subjective symptoms and a measured low blood glucose. Three cases are particularly interesting due to short latencies, (Case E), a positive rechallenge (Case A) and an objectified increase in insulin need (Case C).

Three patients (C, D, E) have been diagnosed with type 2 diabetes, so other DM-related factors cannot be excluded. No indication of other alternative causes like excessive use of alcohol or salicylates was reported. Two patients involved had no history of diagnosed diabetes mellitus (A and B). However in both patients, glucose metabolism and counter balancing hepatic function may have been altered. Patient B is diagnosed with a chronic liver disease. Patient B has been shown to have an impaired glucose metabolism with a HbA1C slightly above reference levels (4.0-5.9%) and increased glucose levels in both postprandial and sober state.

Causality assessment in Case D is complex. Patient D was known with recurrent urinary tract infections not responsive to several antibiotics, however without indication of complications which may lead to hypoglycaemia. Norfloxacin has been used in a prior antibiotic course without inducing hypoglycaemia. Since blood glucose levels were fluctuating over a prolonged period, it is difficult to assess the contribution of norfloxacin to decreased glucose levels. Weeks after the event patient died unexpectedly due to a cerebrovascular accident. No blood glucose levels after norfloxacin treatment were accessible to reporter.

Other sources of information

SmPC

Hypoglycaemia is not mentioned in the Dutch norfloxacin SmPCs. However in the US SmPC, the warning is given to use norfloxacin with caution because of an increased hypoglycaemic risk in patients using glibenclamide [11].

Literature

Despite extensive coverage of hypoglycaemia related to other fluoroquinolones, no publications on norfloxacin-induced hypoglycaemia are accessible through Medline.

Databases

Hypoglycaemia associated with norfloxacin use is disproportionately present in the Netherlands Pharmacovigilance Centre database on August 3rd 2010. The World Health Organization (WHO) pharmacovigilance database however did not support causality on November 4th 2010. Results are shown in Table 2.

Table 2. Reporting odds ratios of norfloxacin and hypoglycaemia in the Netherlands' and WHO Pharmacovigilance database.

Drug and ADR	Number of reports	ROR (95% CI)
Lareb database	5	5.3 (2.2-13.0)
WHO database	18	0.6 (0.4-1.0)

On August 3rd the Eudravigilance database contained two serious reports of hypoglycaemia associated with norfloxacin use and one of a hypoglycaemic coma. One case was deemed life threatening but causality was blurred by the presence of an insulinoma. The second case led to the death of an eighty-year old female with an insulin dependent form of diabetes. An additional twelve preparations including insulin, pioglitazone and glibenclamide were also suspected. The case of a hypoglycaemic coma occurred in an 81-year old female, also known with insulin dependent diabetes. Insulin and pioglitazone were listed under the additional suspect medications.

Prescription data

The number of patients using norfloxacin in the Netherlands is shown in table 3.

Table 3. Number of norfloxacin users in the Netherlands between 2005 and 2008 [6]

Drug	2005	2006	2007	2008
Norfloxacin	125,220	130,220	123,080	118,890

Mechanism

Serum glucose regulation is a complex process in which insulin secretion and counteracting balances lead to a tight regulation of serum glucose levels. Both in in-vitro and in animal studies, fluoroquinolones had inhibitory effects on the ATP-sensitive K⁺ channels in pancreatic β cells, which regulate insulin secretion. This effect is similar to the acting mechanism of sulfonylurea antidiabetics and leads eventually to increased insulin secretion [8]. Quinine which contains a quinolone group is believed to have similar effects exerted through its quinolone component. Normally, hypoglycaemia due to increased insulin secretion, is counterbalanced by molecules acting opposite to insulin like glucagon, however in people with an altered glucose homeostasis, as in type 2 diabetes or hepatic disease, symptomatic hypoglycaemia may develop due to an impaired compensatory function [7].

Discussion and Conclusion

Norfloxacin-induced hypoglycaemia is supported by five reports and is disproportionately present in the Netherlands Pharmacovigilance Centre Lareb's database. Two patients involved had no history of diagnosed diabetes mellitus. Conversely, this association is not disproportionately present in the database of the World Health Organisation (WHO), where the reported numbers indicate a 'protective effect'.

Hypoglycaemia due to some fluoroquinolones is well established in literature and is supported by a plausible mechanism. In addition to the reports about norfloxacin, Lareb has received reports of hypoglycaemia in association with moxifloxacin (1 report), ciprofloxacin (1 report) and levofloxacin (1 report). The potential to induce hypoglycaemia differs between fluoroquinolones and due to the

absence of reports in literature, norfloxacin is likely to be one of the fluoroquinolones with a lesser potential to induce hypoglycaemia. Attention of norfloxacin-induced hypoglycaemia is warranted, including mentioning of glucose lowering effects in the SmPC.

- Attention of norfloxacin-induced hypoglycaemia is warranted

References

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This signal has been raised on November 2010. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).