Contents lists available at ScienceDirect

Primary Care Diabetes

journal homepage: http://www.elsevier.com/locate/pcd

Review

Dysglycemia associated with quinolones

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ARTICLE INFO

Article history:
Received 4 August 2014
Accepted 29 October 2014
Available online 23 November 2014

Keywords:
Hypoglycemia
Hyperglycemia
Antibiotic

ABSTRACT

Antimicrobial therapy is well known to be associated with fluctuations of blood glucose levels. This review aims at exploring the association between glycemic fluctuations and antibiotics mainly focusing on quinolones. Quinolones are associated with hypoglycemia and hyperglycemia. Several mechanism are proposed to explain this causality.

Contents

1. Introduction

Antimicrobial therapy is widely used as part of treatment of outpatient or inpatient infectious diseases. Whether through parenteral or enteral routes, antibiotics are well known to have a wide range of adverse events, namely blood glucose disturbances. In addition, severe infections can predispose patients to both hypoglycemia and hyperglycemia. Dysglycemic events were found to occur with several classes of antibiotic use and are not restricted to diabetic patients.

2. Methods

We searched Medline for literature published on fluoroquinolone-associated dysglycemia with no time limit starting

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http://dx.doi.org/10.1016/j.pcd.2014.10.006
1751-9918/

1946 until present. We used the following MESh to search separately for hyperglycemia and anti-bacterial agents, and hypoglycemia and anti-bacterial agents. The first search lead to 189 articles and the second to 207 articles. Screening and selection of the relevant articles narrowed the search to a total of 91 articles.

The fluoroquinolone antibiotics are widely used because they are generally well tolerated and have a broad spectrum of activity. They can have severe adverse effects, such as potentially fatal ventricular arrhythmias from prolongation of the QT interval, or significant drug interactions, such as with digoxin or warfarin [1,2].

Fluoroquinolones in general and gatifloxacin in particular have been extensively reported in the literature to cause dysglycemia. This seems to be a dose-related adverse effect [3].

The risk of a clinically relevant dysglycemic event appears to vary among the fluoroquinolones.

Gatifloxacin was found to cause dysglycemia at a rate of 1.1%, requiring hospitalization for a considerable proportion of patients. US Food and Drug Administration also issued a report about gatifloxacin causing dysglycemia 56 times more than other fluoroquinolones with rates of hypoglycemia reaching 2%.

In March 2006, FDA required the manufacturer to revise the prescribing information to include a contraindication to the use of gatifloxacin in patients with diabetes and to strengthen the warning that use of gatifloxacin should be closely monitored in patients without diabetes, with a special attention to elderly and those with renal dysfunction [4], and then 2 months later it was withdrawn from the market.

In addition, Canada issued a report of 28 cases gatifloxacin-associated dysglycemia, with 2 deaths.

The odds of severe hypoglycemia and hyperglycemia were significantly greater with gatifloxacin and levofloxacin than with azithromycin. In a retrospective cohort, the incidence rates for severe hypoglycemia and hyperglycemia among those who received gatifloxacin, levofloxacin, ciprofloxacin, and azithromycin were highest for the groups receiving both gatifloxacin and levofloxacin with an incidence reaching 0.35 and 0.45 cases per 1000 patients respectively and higher among patients with diabetes [5]. Ciprofloxacin, levofloxacin and moxifloxacin were also associated with hypoglycemia at a lower rate ranging between 0.2 and 0.3%.

In a retrospective chart review of hospitalized patients 101 patients out of 17,000 charts reviewed were shown to have hyperglycemia or hypoglycemia within 72 h of quinolones administration. The majority experienced hyperglycemia (92 out of 101 patients) rather than hypoglycemia [6].

2.1. *Hypoglycemia*

Gatifloxacin (Tequin) is an 8-methoxy-fluoroquinolone with a wide spectrum of activity against gram-positive, gram-negative, and atypical organisms. Several reports documented increased frequency of hypoglycemia with the use of gatifloxacin. Most of them occurring in nondiabetic patients [7–10].

A case control study involving 788 patients admitted to the hospital for the treatment of hypoglycemia within 30 days of receiving a fluoroquinolones macrolide or second generation cephalosporins showed the highest rate of hypoglycemic events with an adjusted odds ratio of 4.3 for fluoroquinolones specifically gatifloxacin when compared to macrolide. Levofloxacin had an associated odds ratio of 1.5 for the occurrence of hypoglycemia. No increased risk was reported for moxifloxacin, ciprofloxacin, or second-generation cephalosporins [11–13].

Another case control study involving 7287 patients who received gatifloxacin or levofloxacin, 1.6% of the patients recorded hypoglycemia, as early as 1 day. The number needed to harm for gatifloxacin compared with levofloxacin to have 1 additional hypoglycemic event was 101 [14].

A randomized, double-blind, placebo-controlled study, involving 48 patients with type 2 diabetes mellitus who received gatifloxacin or ciprofloxacin or placebo showed no significant effect on glucose tolerance or pancreatic beta cell function. An increase in serum insulin levels, and a decrease in fasting glucose levels up to 6 h after gatifloxacin administration during the first 10 days of treatment was observed but it did not reach statistical significance when compared to placebo. Similar results are shown for ciprofloxacin [15].

A second randomized, double-blind, placebo-controlled trial was performed on 40 healthy men randomized to receive variable doses of intravenous gatifloxacin. Mean change in oral glucose tolerance test and in fasting serum glucose, insulin, and c-peptide concentrations were not different in patients who received gatifloxacin from those who received placebo. Mild transient decrease in serum glucose levels were noted at the completion of a 1 h infusion of gatifloxacin [16].

Renal failure, sepsis, concomitant hypoglycemic therapy mainly sulfonylurea and advanced age were associated risk factors, and significantly predicted hypoglycemia within 96 h.

2.2. *Hyperglycemia*

Gatifloxacin was also associated with hyperglycemia [4,8,17]. It was shown to have the highest risk with an adjusted odds ratio of 16.9 vs a macrolide. No increased risk was detected for levofloxacin, moxifloxacin, or ciprofloxacin in the case controlled trial mentioned previously [12]. Severe hyperosmolar nonketotic hyperglycemia was reported in two nondiabetic patients with liver disease after treatment with gatifloxacin with blood glucose level reaching 942–1456 mg per deciliter [18].

It was also reported to occur in a nondiabetic elderly patient with progressive renal dysfunction receiving a renal adjusted dose of gatifloxavin whose blood glucose level reached 1121 mg dL [19].

Others classes of antimicrobials were found to be associated with dysglycemia such as macrolides with an incidence of 0.1%

Hyperglycemia was shown to occur mostly in patients with non-insulin-dependent diabetes mellitus elderly and those with mild-to-moderate renal insufficiency [20].