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REVIEW ARTICLE

Dysglycemia Associated With The Use Of Fluoroquinolones- Focus On Gatifloxacin

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ABSTRACT

Fluoroquinolones are generally regarded as safe antimicrobial agents with relatively few adverse effects or drug interactions. Dysglycemia (hypo or hyperglycemia) has been reported rarely with many of the fluoroquinolones. The latest data suggests that gatifloxacin is one of the newer fluoroquinolones and is associated with a higher incidence of dysglycemic effects. The exact mechanism behind this effect is not known. The risk factors for the development of this effect are identified as diabetes mellitus, older age, renal insufficiency, and patients taking medications for diabetics (especially hypoglycemic agents). Potential for this increased risk of serious glucose abnormalities should be considered especially while using gatifoxacin in the identified risk groups.

Key Words: Gatifloxacin, fluoroquinolone, dysglycemia, hypoglycemia, hyperglycemia

Introduction

Fluoroquinolones are among the most widely prescribed antibiotics especially for respiratory and urinary tract infections. They are generally regarded as safe drugs associated with mild gastrointestinal and CNS symptoms [1],[2],[3]. Recent events have brought new attention to quinolone safety. Four quinolones have been withdrawn from the US market: temafloxacin, as a result of hemolysis, renal failure and hypoglycemia; trovafloxacin, as a result of hepatotoxicity; grepafloxacin, as a result of torsades de pointes; and sparfloxacin as a result of phototoxicity and torsades de pointes [4].

The latest safety concern regarding the use of quinolones includes associated dysglycemic effects. Dysglycemia (hypo or hyperglycemia) has been reported rarely with many of the fluoroquinolones [5]. However, published case reports and databases of adverse drug reactions (ADRs) and certain studies recently conducted suggest that dysglycemia is more common with gatifloxacin than with other fluoroquinolones [4],[5],[6],[7].

Gatifloxacin is one of the newer broad spectrum fluoroquinolones available and was approved by the US food and drug administration in December 1999 [8]. Ever since its release in the market, there have been numerous reports implicating gatifloxacin as a cause of hypoglycemia and hyperglycemia. This prompted Bristol-Meyer Squibb Co. to list diabetes mellitus as a contraindication to gatifloxacin use in the US product labeling [9] and Health Canada to issue an advisory against the use of gatifloxacin in patients with diabetes [10].

Mechanism

Even though it is not yet well established how fluoroquinolones cause hyperglycemia, investigations have identified a possible mechanism of fluoroquinolone induced hypoglycemia. In vitro experiments have revealed that fluoroquinolones can stimulate insulin release and subsequently hypoglycemia by blocking the ATP-sensitive potassium channels of pancreatic cells [11],[12]. It can trigger the vacuolation of pancreatic beta cells and subsequently lead to reduced insulin levels and hyperglycemia [6],[7],[11],[12],[13].

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Evidence

Evidence that gatifloxacin causes dysglycemia effects in humans includes case reports and small studies in healthy volunteers or hospital inpatients [6]. Further, recently there is evidence from more systematically conducted studies in larger population [4],[6],[7]. Two population-based case control studies were conducted by Park-Wyllie et al [6] in a population of approximately 1.4 million. In Ontario in Canada, residents 66 years of age or older were studied to examine dysglycemia including the related health outcomes associated with various antibiotics received on an outpatient basis (macrolide, a second-generation cephalosporin or respiratory quinolone; gatifloxacin, levofloxacin, moxifloxacin, or ciprofloxacin). Based on the results, the authors concluded that compared to other antibiotics analyzed in the study, the use of gatifloxacin among outpatients is associated with an increased risk of in-hospital treatment for hypoglycemia and hyperglycemia. The risk was similar regardless of the presence or absence of diabetes. With the exception of a slight increase in the risk of hypoglycemia with levofloxacin, these risks were not shared by other fluoroquinolones.

Frothingham compared the rates of glucose homeostasis abnormality and adverse event reports associated with the use of gatifloxacin and other quinolones (ciprofloxacin, levofloxacin, and moxifloxacin) based on the spontaneous reports received by the US Food and Drug Administration between November 1997 and September 2003 [4]. It was noticed that gatifloxacin was associated with 80 per cent of all glucose homeostasis abnormality reports among the various antibiotics evaluated. The authors reported that the rate of glucose homeostasis abnormalities with gatifloxacin was at least ten-fold higher than the rate associated with any of quinolone comparators. The use of gatifloxacin was associated with 453 glucose homeostasis abnormality adverse event reports that included 17 reports with fatality. Patients with the events were older and more likely to be receiving concomitant treatment for diabetes. However, this study had the limitation that it was purely based on data from spontaneous adverse event reporting. This is both incomplete and potentially biased.

Mohr et al [7] conducted a retrospective chart review to compare the rates of blood glucose abnormalities in hospitalized patients receiving fluoroquinolones (gatifloxacin, levofloxacin, ciprofloxacin) or ceftriaxone among 17108 patients. According to the results, dysglycemia was greater in those receiving levofloxacin or gatifloxacin than in those receiving ciprofloxacin or ceftriaxone. However, no difference was noted in the rate of glucose abnormalities with gatifloxacin versus levofloxacin. The events were more frequent in patients with diabetes mellitus or those receiving sulfonylureas.

Pattern and practice implications

Based on the case reports and studies conducted, it was observed that dysglycemia occurred more frequently in elderly patients and diabetic patients (even though the same has been reported in non-diabetic patients). In the published reports, hypoglycemia occurred in the first two days after administration of gatifloxacin and hyperglycemia occurred on days 2-6 [4]. Even though dysglycemia does not appear to be a common manifestation, it is quite significant. This is because the reports included fatal cases as well as serious ones that required additional treatment for the management of the adverse event. Although the risk seems to be significantly high with gatifloxacin compared to other fluoroquinolone antibiotics, it is worthwhile to note that dysglycemia has been reported rarely with other fluoroquinolones especially levofloxacin and ciprofloxacin [4],[5],[14].

The risk factors for dysglycemia have been identified as diabetes mellitus, older age, renal insufficiency, and patients taking medications for diabetics (especially hypoglycemic agents). Appropriate dosage reduction in patients with renal dysfunction and cautious use in elderly patients needs to be considered [13],[14],[15]. Alternatives to gatifloxacin in patients with diabetes appeared to be a wiser decision [1].

Conclusion

Based on the available evidence, a strong association between the use of gatifloxacin and the occurrence of dysglycemia is noted. Potential for this increased risk of serious glucose abnormalities should be considered especially while using gatifloxacin in the identified risk groups.

Conflict of Interest: None declared

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