

The correlation between gatifloxacin's acute adverse reaction and intravenous drip velocity

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ABSTRACT

الأهداف: التحقق من العلاقة بين الرد فعل سلبي (AAR) والسرعة بالتنقيط (جاتيفلوساسين) في الوريد.

الطريقة: اشتملت هذه الدراسة على المرضى الذين تلقوا الحقن (0.2 جرم\100 ملم) في مركز الطوارئ، مستشفى جونان، جامعة وهان، الصين خلال الفترة من يناير حتى أغسطس 2012م وتم تقسيم المرضى عشوائياً إلى 3 مجموعات وفقاً لسرعات المختلفة بالتنقيط كالتالي: مجموعة (A) تلقت 10 قطرات في الدقيقة الواحدة، مجموعة (B) تلقت 20 قطرات في الدقيقة الواحدة، مجموعة (C) تلقت 30 قطرات في الدقيقة الواحدة، وفي الأخير تم توثيق AAR و البيانات الديموغرافية من المرضى.

النتائج: أن AAR من الجلد و الجهاز الهضمي مرتبط بشكل ملحوظ و بشكل ايجابي بسرعة التنقيط في الوريد. ظهرت علاقة AAR في نظام القلب والأوعية الدموية في زيادة سرعة التنقيط في الوريد حين يتجاوز 20 قطرات في الدقيقة الواحدة. أن AAR من الجهاز العصبي و استقلال الجلوكوز ليس له ارتباط كبير مع سرعة بالتنقيط في الوريد من (جاتيفلوساسين).

خاتمة: أن AAR من الجلد والجهاز الهضمي والجهاز القلبي الوعائي يكون انخفاض سرعتهما مناسبة مع الوريد (جاتيفلوساسين) (0.2 جرم\100 ملم) الذي هو أقل من 10 قطرات في الدقيقة الواحدة.

Objectives: To investigate the correlation between acute adverse reaction (AAR) and intravenous drip velocity of gatifloxacin.

Methods: Patients who had received intravenous gatifloxacin (0.2g/100ml) infusion in the Emergency Center, Zhongnan Hospital, Wuhan University, Wuhan, China from January to August 2012 were enrolled in this study. Patients were randomly divided into 3 groups according to different drip velocities: Group A: velocity ≤ 10 drops per minute; Group B: < 10 velocity ≤ 20 drops per minute; Group C: < 20 velocity ≤ 30 drops per minute. The AAR and demographic data of patients were documented.

Results: Acute adverse reaction of the skin and digestive system were significantly positively related to intravenous drip velocity. The AAR of the cardiovascular system significantly increased when the intravenous drip velocity was beyond 20 drops per minute. The AAR of nervous system and abnormal glycometabolism has no significant correlation with intravenous drip velocity of gatifloxacin.

Conclusion: Acute adverse reactions of skin, digestive system, and cardiovascular system would decrease with an appropriate velocity of intravenous gatifloxacin (0.2g/100ml) less than 10 drops per minute.

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Gatifloxacin is a new, advanced-generation, 8-methoxy fluoroquinolone with an expanded spectrum of activity encompassing both gram-positive and gram-negative organisms.¹ It was widely used in the treatment of respiratory system, urinary system, digestive system, skin and soft tissue and gynecology, ophthalmology, otolaryngology infections, and as tuberculosis treatment combination therapy. Although previous study showed that intravenous Gatifloxacin

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injection was safe and well tolerated, the acute adverse reaction (AAR) reports increased with its wide application.² Reactions of the gastrointestinal tract, the central nervous system (CNS) and the skin are the most often observed adverse effects.³ Over the years, several structure-activity and side-effect relationships have been developed, in an effort to improve overall antimicrobial efficacy while reducing undesirable adverse effects. However, the role of drip velocity has not been investigated. The objective of our study was to evaluate the possible correlation between the incidence of gatifloxacin's AAR and its intravenous drip velocity.

Methods. From January to August in 2012, 1868 patients (18-60 years old) who had received intravenous gatifloxacin (0.2g/100ml) injections in the Emergency Centre, Zhongnan Hospital, Wuhan University, Wuhan, China were enrolled in this study. Patients with diabetes, chronic kidney disease and allergy reactions were excluded. The research committee of Zhongnan hospital affiliated to Wuhan University approved this observational study. The velocity of intravenous drip should be controlled at less than 30 drops per minute according to the instruction of gatifloxacin injection.

Patients were randomly divided into 3 groups according to different drop velocity: Group A: velocity ≤ 10 drops per minute; Group B: <10 velocity ≤ 20 drops per minute; and Group C: <20 velocity ≤ 30 drops per minute. The AAR and demographic data of patients were documented. If AAR occurred, the symptom of AAR should be documented, the patients who may have abnormal glucose metabolism should check the blood glucose and the patients who have cardiovascular adverse reactions should receive electrocardiogram test immediately.

Statistical analysis. We used the Statistical Package for Social Science Versus 13.0 (SPSS Inc., Chicago, IL., USA) software for statistical analysis. Chi-square test was used to compare the difference between groups. A *p*-value less than 0.05 was considered significant.

Results. There were 76 patients excluded due to diabetes, nephritis or the age above 60 years old. A total

of 1792 patients were enrolled in this study: Group A (n=565), Group B (n=806), Group C (n=421) (male 1067 and female 725). The symptoms of patients with skin AAR were rash, itching and skin flushing, especially in infusion limb. The symptoms of patients with digestive system AAR were nausea, vomiting, abdominal pain and diarrhea. The symptoms of patients with cardiovascular system AAR were palpitations, chest tightness, arrhythmia and Q-T Interval prolongation. The symptoms of patients with abnormal glucose were hyperglycemia and hypoglycemia. The symptoms of patients with nervous system AAR were dizziness, headache, and hallucination. The number of patients with skin and digestive system AAR in Group C were significantly higher than that in the Groups A and B. Moreover, the number of patients in Group A who had skin and digestive system AAR was less than that in the Group B. The patients with cardiovascular system AAR in the Group C were significantly more than the Groups A and B. However, there were no differences between Groups A and B. The patients with abnormal glucose and nervous system AAR were similar among Groups A, B, and C. The total number of patients with AAR in Group C were significantly more than Groups A and B and Group A were lower than Group B (Table 1). There were no difference between male and female patients.

Discussion. With the ability of inhibiting bacterial DNA gyrase and topology isomerase, Gatifloxacin antibacterial activity can inhibit bacterial DNA replication, transcription and repair process. Gatifloxacin is widely used due to its high selectivity and sterilization.⁴ With the increasing ADR cases of injecting Gatifloxacin in clinical, especially AARs of intravenous gatifloxacin injection, the cases were widely reported around the world, which commonly presented in the skin, abnormal glucose metabolism, cardiovascular system, digestive system and the nervous system.⁵⁻⁷ The mechanism of adverse reactions was numerous. Due to the high drug fat-soluble, it can easily pass through the blood-brain barrier. The combination of its metabolites and γ -amino-butyric acid may cause neurological symptoms.

Table 1 - The result of acute adverse reaction (AAR) in the 3 groups.

Groups	Total N=1792	Skin system	Digestive system	Cardiovascular system	Nervous system	Abnormal glucose	Overall
A	565	4 ^{b,c}	4 ^{b,c}	8 ^a	3	5	22 ^{b,c}
B	806	18 ^a	21 ^a	14 ^a	5	8	63 ^a
C	421	29	23	17	2	4	62

^a*p*<0.05 versus group C, ^b*p*<0.01 versus group C, ^c*p*<0.05 versus group B

Meanwhile, the drug is excreted primarily through the kidney. So the older and renal dysfunction patients prone to adverse reactions.^{8,9} It is reported that gatifloxacin can also inhibit pancreatic β -cell ATP-sensitive K⁺ channel to promote the release of insulin, causing abnormal glucose metabolism. With their unstable glucose metabolism, diabetes patients are more prone to glucose metabolism disorders.¹⁰ Because gatifloxacin's poor water-soluble, intravenous formulations regularly used excipients such as hydrochloric acid, sodium di-hydrogen phosphate, lactic acid to dissolve the drug, these excipients may also produce adverse reactions. Clinical observation showed that slowing down intravenous drip speed might reduce adverse reactions. The results of this study also showed that skin and acute digestive system adverse reactions have a significant correlation with the drip speed. The slower drip speed reduced the incidence of AARs. When the drip speed is more than 20 drops per minute, AARs of cardiovascular system increased significantly. There was no significant correlation between the drip speed and the incidence of nervous system adverse effects and glucose metabolism disorders. Moreover, there was no significant difference between male and female with incidence of AAR. Overall, AAR had a significant correlation with intravenous drip speed. Therefore, appropriate velocity of intravenous drip can reduce the incidence of the AAR of gatifloxacin, especially in skin, digestive system and cardiovascular system. However, AARs of nervous system and glycometabolism do not have remarkable relativity with intravenous drip velocity.

Study limitations. Some patients were injected other drugs at the same time, other drugs may affect the incidence of AAR and some patients change the drip speed by themselves. All these factors will affect the

results of the study; thus, only patients who received intravenous injections of gatifloxacin and who use the infusion pump to inject were included in the study.

In conclusion, acute adverse skin reaction, digestive system, and cardiovascular system would decrease by an appropriate velocity of intravenous gatifloxacin (0.2g/100ml) less than 10 drops per minute.

References

1. Bauernfiend A. Comparison of the antibacterial activities of the quinolones Bay 12-8039, gatifloxacin (AM 1155), trovafloxacin, clinafloxacin, levofloxacin, and ciprofloxacin. *J Antimicrob Chemother* 1997; 40: 639-651.
2. Gajjar DA, LaCreta FP, Uderman HD, Kollia GD, Duncan G, Birkhofer MJ, et al. A dose-escalation study of the safety, tolerability, and pharmacokinetics of intravenous gatifloxacin in healthy adult men. *Pharmacotherapy* 2000; 20: 49S-58S.
3. De Sarro A, De Sarro G. Adverse reactions to fluoroquinolones. an overview on mechanistic aspects. *Curr Med Chem* 2001; 8: 371-834.
4. Hosaka M, Yasue T, Fukuda H, Tomizawa H, Aoyama H, Hirai K. In vitro and in vivo antibacterial activities of AM-1155, a new 6-fluoro-8-methoxy quinolone. *Antimicrob Agents Chemother* 1992; 36: 2108-2117.
5. Mehlhorn AJ, Brown DA. Safety concerns with fluoroquinolones. *Ann Pharmacother* 2007; 41: 1859-1866.
6. Frothingham R. Glucose homeostasis abnormalities associated with use of gatifloxacin. *Clin Infect Dis* 2005; 41: 1269-1276.
7. Jain S, Agarwal J, Laskar S, Gupta T, Shrivastava S. Radiation recall dermatitis with gatifloxacin: a review of literature. *J Med Imaging Radiat Oncol* 2008; 52: 191-193.
8. Blommel AL, Lutes RA. Severe hyperglycemia during renally adjusted gatifloxacin therapy. *Ann Pharmacother* 2005; 39: 1349-1352.
9. Stahlmann R, Lode H. Safety considerations of fluoroquinolones in the elderly: an update. *Drugs Aging* 2010; 27: 193-209.
10. Saraya A, Yokokura M, Gono T, Seino S. Effects of fluoroquinolones on insulin secretion and beta-cell ATP-sensitive K⁺ channels. *Eur J Pharmacol* 2004; 497: 111-117.

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