Title

The clinical value of penicillin G outweighs its usage restriction due to a too-much concern for hyperkalemia

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Manuscript

The promotion of antimicrobial stewardship, which applies to activities related to sustainable development goals, should be a top priority in this era of antimicrobial resistance (AMR) [1]. Narrow-spectrum antimicrobials can reduce the risk of developing antimicrobial resistant organisms by preserving the use of broad-spectrum antimicrobials. Among the various antimicrobial agents, penicillin is mainly active against gram-positive bacteria and has no superfluous covering spectrum, being one of the narrowest antimicrobial agents in clinical use [2].

Since its discovery, manufacturing, and clinical use in 1940s, penicillin, also referred to as the "magic bullet," has saved uncountable lives [3]. Of the several forms, penicillin G (PCG, known as pottasium benzylpenicillin) is available in Japan. With increased clinical use, penicillin resistance has occurred in many pathogenic organisms as a consequence of molecular changes in penicillin-binding proteins, production of β-lactamases, and overexpression of porin proteins and/or efflux pumps [4]. However, penicillin is still recommended as a first-line therapeutic option for a wide variety of infectious diseases, including streptococcal infections (*Streptococcus pneumoniae* pneumonia and meningitis, viridans-streptococcal infective endocarditis, and necrotizing fasciitis due to beta-hemolytic streptococcus), spirochetal infections (syphilis, leptospirosis, and Lyme disease), actinomycosis, and *Clostridium*

perfringens infection [5].

Despite its clinical effectiveness and advantage in antimicrobial stewardship, PCG imposes a risk of hyperkalemia due to its potassium (K^+) salt preparation form. Notably, one vial of PCG comprises 1 million units (MU), which contains 1.53 mEq of K^+. Furthermore, the maximum dosage of PCG is 24 MU (4 MU [that is, 6.12 mEq of K^+] every 4 h), which results in a dose of approximately 36.7 mEq of K^+ per day. Detailed pharmacokinetics of serum or urine K^+ levels related to PCG administration are not available in the literature; however, there have been reports of sudden death involving patients undergoing PCG therapy [6]. Thus, appropriate serum K^+ level monitoring is required, especially in patients with renal dysfunction (creatinine clearance $\leq$50 ml/min), those with prolonged PCG treatment, those with any underlying cardiac diseases that possibly cause arrhythmia, and those prescribed other drugs that may cause K^+ elevation, such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, cyclosporine, tacrolimus, spironolactone, and so on.

In general, medical institutes establish standards for intravenous K^+ supplementation from medical safety perspectives. Here is an example of potassium-containing intravenous formulations; (i) Formulations containing K^+ above 40 mEq/L should not be administered in general wards, (ii) The dosing speed should be less than 10 mEq/hr of K^+, and (iii) The total daily dose of K^+ should not exceed 100 mEq. **Table 1** summarizes the K^+ compound contents in

each dosage and formulation of PCG. Antimicrobial agents are mostly administered after being dissolved in 100 mL of normal saline or a glucose solution. In such cases, 3 and 4 MU PCG contain 45.9 mEq/L and 61.2 mEq/L of K^+, respectively, being incompatible with the hospital rules. When diluted two-fold, using 200 mL of solvent, the K^+ concentration of 4 MU PCG decreases to 30.6 mEq/L. However, increased fluid volume (1,200 mL per day) may not be acceptable in patients with heart failure; common clinical scenario are cases of post-cardiac surgery for infective endocarditis. In addition, even the double-diluted solution cannot meet the criteria for dosing speeds of less than 10 mEq/h. Overcoming this requires 3 hours or more for each infusion and, consequently, 18 hours or more as a daily infusion. Extending this concept, continuous administration has been widely adopted for PCG treatment [7]. Bryan *et al.* proposed an optimum high-dose PCG therapy as a continuous infusion of 10 to 12 MU of PCG (every 12 h) after a 3 MU loading dose, which can achieve a serum penicillin level of 16 to 20 μg/mL [8]. To abide by the standards for K^+-containing intravenous formulations, the following regimen would be reasonable in our settings; 12 vials of PCG are diluted with 500 mL of a solvent and infused in 12 hours, which allows the K^+ concentration and dosing speed to reach 36.72 mEq/L (< 40 mEq/L) and 3.06 mEq/hr (<10 mEq/hr), respectively.

As discussed, a high-dose PCG therapy violates hospital regulations for K^+-containing formulations and thus, cannot be considered for patients who require such treatment. However,

considering several aspects, such as its clinical efficacy as an antimicrobial agent, symbolic position as a representative drug for antimicrobial stewardship, and educational purposes for infectious disease treatment, excessive clinical use restriction due to hyperkalemia concerns are unacceptable. We highlight the great importance of developing a therapeutic strategy to safely provide PCG treatment for each patient. Physicians are expected to administer the classic, but still active, antimicrobial drug wisely, carefully, and safely.

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Conflict of interests

None to report.

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