Penicillin G benzathine: characteristic of prescription and use in community pharmacy

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ABSTRACT. The use of antimicrobial substances must be determined by a knowledge of principles ranging from their chemical composition, pharmacokinetic and pharmacodynamic characteristics, adverse effects and doses, to the means and intervals in their administration. It is the possible method to establish secure and efficacious therapeutic regimens to solve an infection condition. Lack of knowledge of these principles concerning Benzathine Penicillin G in community pharmacy is evident. Results show the need for retraining and updating health professionals in the rational use of this antimicrobial agent.

Key words: antimicrobials, benzathine penicillin, penicillin G.

RESUMO. Penicilina G benzatina: características de prescrição e uso na farmácia comunitária. A utilização dos antimicrobianos deve ser regida pelo conhecimento de princípios, que vão da composição química, características farmacocinéticas e farmacodinâmicas, efeitos adversos e dose, até vias e intervalos de administração. Desta forma, é possível estabelecer esquemas terapêuticos seguros e eficazes para a resolução do quadro infeccioso. No presente estudo foi avaliada a utilização da penicilina benzatina em farmácia comunitária de medicamentos. Os dados foram coletados através de um protocolo, o qual foi preenchido de acordo com as informações dos pacientes. Os resultados obtidos demonstram a deficiência de conhecimento dos princípios que orientam a utilização da penicilina benzatina, bem como a necessidade de reciclagem e atualização dos profissionais de saúde para o emprego racional deste antimicrobiano.

Palavras-chave: antimicrobianos, penicilina benzatina, penicilina G.

The prescription of an antimicrobial agent must be governed by knowledge of certain principles that normally indicate its use. Among these are the chemical composition, mechanism of action, activity spectrum, dose, pharmacokinetics, and cost of therapy. It is also necessary to know a number of factors regarding infectious agents, such as the flora commonly involved in the principal infections, the normal pattern of sensitivity of the microorganism to the antimicrobial agent, the nature of the infection to be treated, and the characteristics of the host that will receive the antimicrobial agent. Knowledge of these principles can guarantee a solution to the infection process (Rocha, 1998).

Penicillin G and its semi-synthetic derivatives are still one of the main groups of antimicrobials used in antimicrobial therapy of the principal infectious diseases. Penicillin G is available in the form of three salts: crystalline penicillin G (sodium or potassium), procaine penicillin G, and benzathine penicillin G. All three formulae have the same active antimicrobial principle. However, due to differences in solubility and consequent variations in serial concentrations, the clinical indications of procaine and benzathine penicillin G are more specific (Amato Neto *et al*., 2000a).

In community pharmacies where the use of stock penicillin is very frequent, variations in the administration intervals of benzathine penicillin G have been observed, even when a medical prescription is extant. The objective of this investigation was to study the manner benzathine penicillin G is used in the public pharmacy, when its pharmacokinetic aspects are taken into account.

Penicillin G (benzylpenicillin) may be administered by oral, intramuscular, and intravenous routes. Preparations administered orally may be inactivated by gastric juices, with consequent

compromise in its absorption. Due to instability in acid medium, penicillin V (phenoxymethylpenicillin) was developed for exclusive oral administration. This form is much more stable in acid medium than penicillin G, and permits greater absorption in the gastrointestinal tract, mainly in the form of potassium salts. An equivalent dose of penicillin V administered orally reaches serum levels 2-5 times higher than penicillin G administered by the same route, and the peak blood concentration in adults following a 500-mg dose is approximately 5 U/ml (Mandell and Petri Jr., 1996).

Since penicillin G has a short half-life, approximately 30 minutes in individuals with normal renal function, it must be administered at four- to six-hour intervals to maintain mean serum concentration (Amato Neto *et al*., 2000b). Due to this characteristic and to minimize the necessity for frequent administration, penicillins for long-term storage or slow release, procaine penicillin G and benzathine penicillin G, were developed. These formulae, administered only intramuscularly, slowly release penicillin G from the injection site, allowing a longer interval between doses and yielding serum levels for a longer period (Mandell and Petri Jr., 1996).

Procaine penicillin G is an aqueous preparation of crystalline salt with 0.4% solubility in water, where the procaine combines mole for mole with penicillin; thus a 300,000 Ul dose contains approximately 120 mg procaine. Its half-life is approximately 12 hours, allowing administration at 12 to 24-hour intervals (Neu, 1995). The same dose of 300,000 Ul administered intramuscularly produces serum levels of approximately 1.5 U/ml over an interval of 1-3 hours. After 24 hours the plasma concentration is reduced to 0.17 U/ml, and after 48 hours to 0.05 U/ml. Higher doses (600,000 Ul) yield slightly higher serum concentrations, maintained for 4-5 days (Mandell and Petri Jr., 1996).

Benzathine penicillin G is an aqueous suspension obtained by combining 1 mole of ammonia base with 2 moles of penicillin G. The salt has low solubility (0.02%/H_2O) which guarantees that penicillin G will remain in the blood for a prolonged period. Nevertheless, the serum concentrations of penicillin G are low compared to those provided by crystalline penicillin G (sodium or potassium) and procaine penicillin G (Mandell and Petri Jr., 1996). The insolubility of benzathine penicillin G is responsible for its long half-life of approximately 336 hours (Neu, 1995). Following intramuscular injection of 1,200,000 UI of benzathine penicillin G in adults with normal renal function, the serum concentration in the 1st hour is approximately 0.11 U/ml. On the 1st day it is 0.08 U/ml, on the 7th day 0.07 U/ml, on the 14th day 0.04 U/ml, on the 21st day 0.03 U/ml, and on the 28th day 0.02 U/ml (Décourt *et al*., 1983), with traces of penicillin G remaining in the blood for more than 30 days following a single intramuscular injection (Décourt *et al*, 1983;Thamlikitkul *et al*., 1992). Researchers have also reported quite similar pharmacokinetic data in children, where the variations were attributed to such factors as the characteristics of the population (age, race, environmental factors, metabolism, etc.), the methods employed, and the origin of the benzathine penicillin G, among others (Lamas *et al*., 1992).

Material and methods

Results were obtained from a community pharmacy and in a health clinic, in the city of Umuarama, state of Paraná, Brazil, from May to December 1998. A data collection form was developed to record information on 117 patients using benzathine penicillin G. Information included medical guidance, diagnostic hypothesis based on patient-given information and administration interval.

Results and discussion

Data obtained in the present investigation demonstrate that most patients who came to the pharmacy for administration of benzathine penicillin G, did so under medical advice. This is a natural and expected procedure, since intramuscular injection of benzathine penicillin G is very painful and normally the patients do not voluntarily opt for its use (Table 1).

Table 1. Consumption of benzathine penicillin G according to source of medical guidance

Guidance	Benzathine penicillin G	
	Number	%
With Medical	83	70.94
Without Medical	34	29.06
Total	117	100.00

The therapeutic indications for benzathine penicillin G (Table 2) were varied, ranging from postoperative use (caesarian, toenail removal, phimosis, appendix), treatment of infections of the upper airways, corn removal, and ovarian infections to bone fractures. Other situations may be included in which normally benzathine penicillin G is not the

appropriate antimicrobial agent because of its pharmacokinetic characteristics.

Table 2. Use of benzathine penicillin G according to medical diagnosis (as referred to by the patient)

Pathology	Frequency	%
Endometritis	1	1.2
Erysipelas	2	2.4
Respiratory Infection	23	2.8
Pharyngitis	4	4.8
Removal of Toenail and Corn	5	6.0
Phlebitis	1	1.2
Postoperative	6	7.2
Otitis	5	6.0
Varix Ulcer	4	4.8
Furunculosis	18	21.7
Gonorrhea	2	2.4
Headache	2	2.4
Fracture	1	1.2
Uterine Wound Cauterization	1	1.2
Sinusitis	1	1.2
Rheumatic Fever	6	7.2
Ovarian Infection	1	1.2

A pertinent observation was the wide variation between administration intervals of benzathine penicillin G. Table 3 shows that 32.53% of the injections were done at 24-hour intervals for periods of up to 6 consecutive days. This plan of administration does not appear to be ideal if we consider that pharmaceutical form is slowly released, and that administration at shorter intervals does not necessarily lead to proportionately higher plasma concentrations, because of its insolubility (Amato Neto *et al*., 2000a, b).

Table 3. Medical prescriptions for benzathine penicillin G

Number of Prescriptions	Intervals between administrations h (hour) d (days)	Period of treatment	%
10	one	–	12.05
4	15 d	60 d	4.85
1	10 d	30 d	1.21
4	5 d	10, 20, 25 d	4.82
19	3 d	6, 9, 12, 15, 18 d	22.89
15	2 d	4, 6, 8 d	18.07
1	36 h	4, 5 d	1.21
27	24 h	2, 3, 4, 5, 6 d	32.53
2	12 h	3 d	2.41

Information about the different serum levels yielded by the stock penicillins is of fundamental importance in selecting one of these salts for the treatment of different infections caused by microorganisms with varying sensitivity to penicillin G.

In the case of *in vivo* effectiveness of penicillin G, it is necessary to determine the minimum inhibitory concentration for the bacteria in question. Adequate therapeutic levels are only obtained with minimum plasma concentrations of approximately 2-3 times the minimum inhibitory concentration (MIC) for the specific microorganism, taking into consideration that the levels at the sites of infection (tonsils, skin, etc.) are sharply lower than serum levels (Toporovski, 1981).

In the case of Streptococcus β-hemolytic A, sensitivity to penicillin G is still satisfactory, with the MIC ranging between 0.009 and 0.01 U/ml (Eickhoff and Maxwell, 1965; Jelinkova and Jelinek, 1965; Chabbert and Horodniceanu, 1975; Chambers and Neu, 1995). Although Tomasz (1994) has isolated penicillin G-resistant Streptococcus, due to the latter's infrequency, penicillin G continues to be the antimicrobial agent of choice in the treatment of streptococcal infections (Pereira, 1996).

The use of benzathine penicillin G is limited to the treatment of infections caused by germs sensitive to low serum concentrations of penicillin G. It should not be used in treatment of infections in which the etiological agent requires a minimum inhibitory concentration (MIC) of penicillin G higher than that provided by benzathine penicillin G (Amato Neto *et al*., 2000 a, b).

When the serum levels of penicillin G yielded by intramuscular injection of a single dose of 1,200,000 UI of benzathine penicillin G (Décourt *et al*., 1983; Mandell and Petri Jr., 1996) and the sensivity of *Streptococcus* (Table 4) are considered, the probable efficiency of a single dose of benzathine penicillin G is established, without the need for successive injections of this penicillin to solve the infection condition in question.

Table 4. Pattern of susceptibility of microorganisms to penicillin G

Microorganisms	Penicillin G minimal inhibitory concentration (U/ml)*
Streptococcus pneumoniae	0.016
Streptococcus pyogenes	0.0083
Streptococcus agalactiae	0.0083
Streptococcus viridans	0.16
Enterococcus faecalis	5.0
Staphylococcus aureus penicilinase (-)	0.033
Staphylococcus aureus penicilinase (+)	>41.6
Staphylococcus epidermidis	0.033
Neisseria gonorrhoeae	0.016
Neisseria meningitidis	0.083
Clostridium perfringens	0.83
Corynebacterium diphtheriae	0.16
Listeria monocytogenes	0.83
Haemophilus influenzae	1.33
Bacteroides fragilis	53.3
Escherichia coli	16.6
Klebsiella spp	>666.6
Enterobacter spp	>833.3
Salmonella	16.4
Shiguella	33.3
Pseudomonas aeruginosas	>833.3

(Modified from Chambers and Neu, 1995) (* 1 U = 0.6 μg)

In a clinical situation in which the infection involves microorganisms that require a very high

MIC of penicillin G, benzathine penicillin G is an inadequate alternative, even with successive doses at short intervals. Under these conditions it is more rational either to use a formulation of penicillin G that immediately yields high serum concentrations, or else to select another antimicrobial agent.

Although the antimicrobials are one of the drug groups most frequently used in daily therapeutics, they are often used incorrectly. In the present study it is clear that the use of benzathine penicillin G in the community pharmacy is appropriate neither to its pharmacokinetic profile nor to the sensitivity of the etiological agents involved in the infection process. It is therefore important that health professionals update the literature describing the ideal conditions for the use of this antimicrobial agent with regard to administration intervals and therapeutic indications for its use in the treatment of different infections.

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