

Correspondence

Clarification concerning amoxicillin skin testing

To the Editor:

Regarding the controversy concerning the solubility of amoxicillin for skin testing,^{1,2} an important misunderstanding exists. Macy states that amoxicillin's solubility in water at pH 7 is 4 mg/mL. Thus, skin testing using 20 mg/mL of amoxicillin is an irritant because it requires a nonphysiologic pH to ensure amoxicillin's solubility in solution.² Macy does not take into account that three forms of amoxicillin exist, with their corresponding Chemical Abstracts Service (CAS) registry numbers.³

The active pharmaceutical principle is the molecule of amoxicillin (CAS 26787-78-0), which provides the antibiotic activity. Based on this, 2 types of amoxicillin are available (Fig 1): the injectable type is a sodium salt (CAS 34642-77-8)³ that can be easily dissolved at physiologic pH in water. In fact, 200 mg/mL is the concentration of amoxicillin allowed for parenteral use and for which complete solubility is necessary in order to avoid adverse effects. The other type is the trihydrate form (CAS 61336-70-7)³ used for oral administration. It displays a carboxylic acid functionality and cannot be easily dissolved in water. The *European Pharmacopeia 5.0* states that the water solubility of these 2 types of amoxicillin is different, with amoxicillin trihydrate described as slightly soluble and amoxicillin sodium as very soluble. The less water-soluble form (trihydrate) is the one Macy has used for skin testing, and it is therefore impossible to reach a concentration of 20 mg/mL. Thus, he wrongly concludes that false-positive data have been reported in most studies.²

Since the 1980s all these considerations have been taken into account, which is why the injectable form of amoxicillin was selected.⁴⁻⁶ This has enabled the diagnosis based on skin test in a considerable number of patients who would otherwise have been missed if this procedure had not been carried out.^{5,6} Based on this evidence, this practice is now recommended by the European Network of Drug Allergy for skin testing at 20 mg/mL.⁶ It is an inexcusable mistake to confuse the 2 structures of amoxicillin even though the difference consists of a single atom, either sodium or hydrogen, that provides the salt and the trihydrate form with their respective properties.

The author has extended the same confusion to ampicillin. Similarly, 3 compounds are registered in CAS,³ corresponding to ampicillin (CAS 69-53-4), the trihydrate form (CAS 7177-48-2), and the sodium salt (CAS 69-52-3). The oral trihydrate form is slightly soluble in water, and the injectable sodium salt is more soluble (50 mg/mL).

There is an effect of pH on solubility. The ionization constants have been calculated for these 2 aminopenicillins.⁷ The pK_a 's of amoxicillin are 2.67, 7.11, and 9.55, whereas the pK_a 's for ampicillin are 2.67 and 6.95. At a pH equal to the isoelectric point, they exist essentially as zwitterions and, in this form, are more stable and less soluble in water. Certainly, different forms of the same chemical compound can exhibit different physical and chemical properties, including different solubility and dissolution profiles, which, in turn, can affect the bioavailability and stability of the drug.

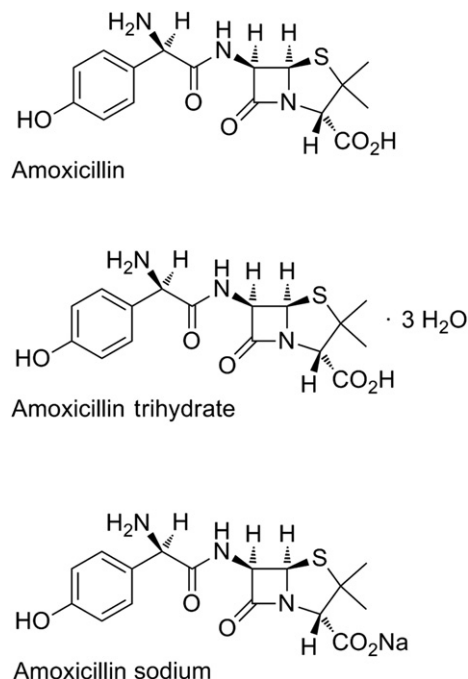


FIG 1. Chemical structures of amoxicillin.

With this correspondence we hope to have clarified this important issue.

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