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Original Article

# Masking of an intravenous preparation of ceftriaxone for use in clinical trials: A technical report

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ABSTRACT

***Background:*** Intravenous antibiotics are often evaluated in clinical trials in hospitalised patients but for blinded trials masking of antibiotics is required.
***Objective:*** To evaluate the effectiveness of masking of ceftriaxone and amoxicillin / clavulanic acid for use in blinded clinical trials.
***Design, setting, and participants:*** Amoxicillin / clavulanic acid (1.2g) and ceftriaxone (1g and 2g) were diluted in 100mL of sodium chloride. Clinicians from a single centre were asked to attempt to distinguish solutions containing antibiotics from solutions without added antibiotics at time points up to 12 hours following dilution.
***Results:*** 1g of ceftriaxone diluted in 100 mL of 0.9 sodium chloride stored in a light-protected bag and refrigerated at 3–4 °C for up to 10 h could not readily be distinguished from 100 mL of 0.9 % sodium chloride. However, solutions containing either amoxicillin / clavulanic acid (1.2g) or ceftriaxone (2g) were readily identifiable.
***Conclusions:*** 1 g of ceftriaxone can be effectively masked by dilution in 100mL of sodium chloride.


## 1. Background and significance

Intravenous antibiotics are often evaluated in clinical trials in hospitalised patients. Blinding is important to strengthen internal validity and to reduce the risk of performance bias in clinical trials. One area where placebo-controlled trials of antibiotics is required is in evaluating the role of antibiotic prophylaxis in preventing ventilator-associated pneumonia in intensive care unit (ICU) patients.

Several small, single centre pilot randomised clinical trials (RCTs)[1,2,3] and a multicentre RCT[4] suggest that prophylactic antibiotics may reduce the occurrence of lower respiratory tract infections in invasively mechanically ventilated ICU patients with acute brain conditions. These trials evaluated ceftriaxone or amoxicillin/clavulanic acid but have not adequately described blinding procedures.

To inform the design of future similar trials, we sought to evaluate whether 1 g, 2 g, ceftriaxone and 1.2 g of amoxicillin/clavulanic acid could be masked by dilution in 100 mL of 0.9 % sodium chloride and whether masking could be sustained with a period of storage.

## 2. Methods

### 2.1. Antibiotic and comparator preparations

In accordance with the guidelines of the respective manufacturers, ceftriaxone 1g (AFT Pharmaceuticals, Auckland, New Zealand), amoxicillin (1g)/clavulanic acid (200 mg) (Multichem, Auckland, New Zealand), and ceftriaxone 2g (AFT Pharmaceuticals, Auckland, New Zealand) were reconstituted in 20 mL, 20 mL, and 40 mL of sterile water for injection (DEMO S.A Pharmaceutical Industry, Athens, Greece). Reconstituted antibiotics were diluted in 100 mL of 0.9 % sodium chloride (Baxter International, Deerfield,

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**Table 1**
Identification of preparations containing antibiotics over time.

| | Correct identifications of solutions containing antibiotics[a] (n/N) | | | |
|---|---|---|---|---|
| | 0hr since preparation of antibiotics | 4hr since preparation of antibiotics | 8hr since preparation of antibiotics | 12hr since preparation of antibiotics |
| Ceftriaxone[b] 1 g | 3/10 | 3/10 | 2/10 | 8/10 |
| Ceftriaxone 2 g | 7/10 | 9/10 | 8/10 | 10/10 |
| Amoxicillin 1 g with clavulanic acid 200 mg | 9/10 | 9/10 | 10/10 | 10/10 |

[a] The number of participants (n) who correctly identified the antibiotic at each time point and the total number of participants (N) at each time point is shown. The ten participants who attempted to identify antibiotics at a particular time point were the same; however, different participants attempted to identify antibiotics at each time point.
[b] 1gm Ceftriaxone was also checked at 10 h after preparation and 3/10 participants correctly identified it.

Illinois, USA). For the ceftriaxone 1g and amoxicillin/clavulanic acid solutions, 20 mL of 0.9 % sodium chloride was removed from a 100 mL 0.9 % sodium chloride bag and discarded; for ceftriaxone 2g solution, 40 mL was removed and discarded. The reconstituted solutions were then added into the corresponding 0.9 % sodium chloride bags via the injection port to give a total volume of 100 mL in each bag.

Comparator fluid bags contained 100 mL 0.9 % sodium chloride (Baxter International, Deerfield, Illinois, USA). The injection ports of these bags were punctured with a blunt fill needle, so the antibiotic and comparator bags were identical in appearance.

Three paired samples were prepared by an unblinded research nurse. Each pair of samples consisted of one of the three antibiotic preparations and a 100 mL bag of 0.9 % sodium chloride for comparison. All bags were stored in a light-protected bag in a refrigerator at 3–4 °C for the duration of the study.

### *2.2. Participating healthcare providers, time points, comparisons, and data collection*

A total of ten healthcare providers evaluated each of the three pairs of antibiotic/comparator fluid bags at 0 h, 4 h, 8 h, and 12 h after preparation of the antibiotics. The ten healthcare providers were different at each time point, meaning a total of forty individuals were involved in the study. Healthcare providers were provided with a pair of fluid bags and asked to determine by visual inspection which contained antibiotic. Possible answers were: “bag A″, “bag B″ and “don't know”. We classified responses as either “correctly guessed the bag, which contained antibiotic” or “did not correctly guess the bag which contained antibiotic”. All responses were captured on Google Forms (Google LLC, Mountain View, California, USA).

### *2.3. Data analysis*

Data from the Google Forms was then extracted and transcribed into Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA) for analysis and graphical display. We report the number and proportion of participants who correctly identified each antibiotic at each time point.

## 3. Results

The number of participants who correctly identified the preparation containing each of the antibiotics is shown in Table 1.

## 4. Discussion

In this study, we evaluated the effectiveness of masking ceftriaxone and amoxicillin/clavulanic acid by dilution in 100 mL of 0.9 % sodium chloride. We observed that at all time points tested except 12 h after preparation, fewer than half of study participants were able to correctly identify the preparation containing 1g of ceftriaxone. Neither 2g of ceftriaxone nor 1g of amoxicillin with 200 mcg of clavulanic acid where effectively masked by dilution in 100 mL of saline as most participants could correctly identify these preparations at all time points.

In our study, correct identification of all antibiotic preparations appeared to increase over time. This observation is consistent with previous work showing observable colour changes with amoxicillin/clavulanic acid over time.[5,6] Such studies also suggest amoxicillin/clavulanic acid degrades substantially over a short period of time (1–2 h) following preparation. In keeping with such data, the New Zealand Medsafe datasheet indicates that reconstituted amoxicillin/clavulanic acid is stable for 20 min at room temperature, and up to 8 h if refrigerated at 5 °C.[7] In contrast, ceftriaxone is stable in solution over a 24h time frame.[5,6] The New Zealand Medsafe datasheet indicates that solutions of ceftriaxone retain physical and chemical stability for 6h at room temperature and for 24h if refrigerated at 2–8 °C.[8]

We acknowledge several limitations. First, quantitative strategies using optical colourimetry or other means would potentially result subtle differences between preparations with and without antibiotics being detectable; however, we considered that a visual inspection provided a reasonable basis to assess masking of preparations for use in multicentre pragmatic trials. Second, only 10 healthcare workers evaluated preparations at each time point; a larger sample size would provide greater certainty in our findings. Third, our findings only apply to specific formulations of antibiotics we have tested; other brands of antibiotics may have different physiochemical properties and stability in solution.

In conclusion, our data suggest that 1g of ceftriaxone diluted in 100 mL of 0.9 sodium chloride stored in a light-protected bag and refrigerated at 3–4 °C for up to 10 h cannot readily be distinguished from 100 mL of 0.9 % sodium chloride. These findings suggest that the method of preparation and storage that we describe could be effectively used to mask study medication (1 g of ceftriaxone or placebo) in a blinded clinical trial. In contrast, neither 2 g of ceftriaxone nor 1 g of amoxicillin/200 mg of clavulanic acid could be effectively masked by this method.

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## CRediT authorship contribution statement

**Golding, Chan:** Writing - original draft, data collection.
**Orozov:** Logistic support, Writing - review and editing.
**Young:** Conceptualisation, Metholodology, Writing - review and editing.

## Conflict of interest

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests: Prof Young serves as an Associate Editor for Critical Care and Resuscitation.

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