ERRATUM: CYCLOPHOSPHAMIDE IN PARAQUAT POISONING

To the Editor:

We have written an Editorial on paraquat intoxication (1), in which we re- view the physiopathology, the prognosis, and the treatment of this intoxica- tion. One of the citations was that of Lin and colleagues, published last year in the AJRCCM (2). In this article spectacular results were obtained with re- spect to patient survival rates, given that some 82% of patients with moder- ate or severe intoxication survived after receiving, among other measures, pulse therapy with glucocorticoid and cyclophosphamide (CP). However, the dose of CP that appears in the mentioned article is much more toxic than the paraquat itself if we go by what is stated in the Methods section, which says that patients received “15 g/kg of CP in 5% glucose saline 200 ml intrave-
nously infused for 2 h/d” for two days. In previous articles by the same group or by other authors doses of 1 g/day or of 15 mg/kg are used (3, 4, 5). In addi- tion, immunosuppressive therapy using high doses of CP do not usually use more than 7 g/m² of body surface (5) or 50 mg/kg/d (6).

For these reasons, we believe that the dose of CP stated in the article must be a typographical error and should read milligrams (mg) instead of grams (g). However, until now this error seems not to have been noticed, or at least we have not seen it corrected in subsequent issues of your journal. We are firmly convinced that the treatment described by Lin will be used in many hospitals throughout the world and cited in textbooks of pneumology, critical care, clinical toxicology, emergency medicine, etc. Therefore, as well as informing Dr. Lin of our observation, we have thought it opportune that the readers of the AJRCCM also be informed on this important point, in order to avoid the possibility of treatment guidelines that could have severe conse- quences for patients suffering from paraquat intoxication.

ERRENTE: CYCLOFOSFAMIDA EN ENPOISONAMIENTO CON PARAQUAT

致编辑

我们已经撰写了一篇关于paraquat中毒的评论（1），其中我们复习了其生理病理学、预后和治疗。其中一位参考文献是林和同事在去年AJRCCM（2）上发表的文章。该文章中，大约82%的患者在中毒后得到存活，尽管按照方法部分所述，CP的剂量远高于paraquat本身的毒性。按照方法部分所述，患者接受“15g/kg的CP在5%葡萄糖溶液200ml中静脉输注2h/d”治疗2天。在以前的文献中，同类研究使用1g/d或15mg/kg（3, 4, 5）。此外，在使用高剂量的CP时，通常不使用超过7g/m²的体表面积（5）或50mg/kg/d（6）。

由于这些原因，我们认为CP的剂量在文章中存在打字错误，应该为毫克（mg）而非克（g）。然而，直到现在这个错误尚未被注意到，或者至少在我们的期刊中尚未看见纠正。我们坚信林教授描述的治疗将被用于许多医院，并会在世界的许多医院中被采用，并被引用在呼吸病学、重症监护、临床毒理学、急诊医学等领域的教科书中。因此，我们也认为读者可能需要告知AJRCCM和其他有关的读者，这非常重要，以避免可能出现的治疗指南，这些指南可能对paraquat中毒患者产生严重的不良后果。

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ATS GUIDELINES FOR METHACHOLINE AND EXERCISE CHALLENGE TESTING

To the Editor:

The Guidelines (1) are timely, useful, and well balanced. However, although they are in general evidence-based, the rationale of some recommendations remains unconvincing.

1. The use of PC20/PD20, including the choice of the highest FEV1 value, is no longer arbitrary. Modeling studies have found that for various physio- logic reasons (2), in populations with partial overlap in bronchial respon- siveness, PD20 by means of the highest FEV1 (PD20h) is more discrimina- torily lower than lower FEV1 endpoints, PD20h by means of the lowest FEV1 (PD20l) or PD20 by means of SGaw (3).

2. The normative data based on tidal volume challenge with histamine (4) cannot be transferred, as proposed by the Guidelines, to the 5-breath challenge with methacholine. First, the difference between histamine and cholinergic responses may exceed one doubling dose either because of host differences (5, 6) or output differences across De Vilbiss 646 nebu- lizer (6, 7). Second, PD20h is predictably higher than PD20l, 1.5 times higher in normals and 1.15 higher in asthmatic subjects (2, 3). Thus, contrary to the statement on p. 317 of the Guidelines (1), PC20h and P20h are not interchangeable for the very reason given on the same page: diagnos- tic methacholine challenge is carried out in patients with mild asthma and quasi-normal response to deep inhalation. Third, methacholine challenge with the rapid, 5-breath method may produce cumulative effects whereas histamine inhalation with the slower, tidal breathing method may not (8); see also p. 317, first paragraph in Reference 1.

3. It is gratifying that the interest sparked by Reference 3 on Bayesian analy- sis is also shared by the Guidelines. However, the analysis of normative data is surprising. First, Fig. 3 (1) is based on three sets of (condensed?) normative data but only one is subsequently discussed and recom- mended. Second, I doubt that the patients that might benefit from metha- choline challenge should be compared with a subset of “current asthma” (4). This small subset (17 subjects!) has 100% pre-test probability of asthma, way outside the recommended range of 30–70%, and 100% posi- tive tests to methacholine. Some disease characteristics that may influ- ence methacholine test results are not specified; e.g., length and severity of disease or treatment. Methacholine challenge is usually performed on oligosymptomatic patients, often with atypical triggers; they seem to re- spond to 2–8 mg/ml methacholine in only 5–14% of the cases (9). More- over, it is inconsistent with Bayes’ theorem to plot on the methacholine curve obtained from normals and the entire asthmatic population, the posttest probability resulting from a pretest probability of a subset of the latter population. The term of comparison for an asthmatic population is not the general population but the asthmatic population with similar asthma characteristics. Consequently, sensitivity, specificity, receiver- operator characteristics (8) and pretest probability should also be differ- ent. Finally, the Guidelines should have mentioned that the population

From the Author:

We appreciated the comments from Dr. Antonio Duenas-Laita and his col- league (1).

Initially, we used pulse therapy with cyclophosphamide (CP) in our pre- vious work (2). The dose of CP was 1 g/d for 2 d and methylprednisolone 1 g/d for 3 d in treating patients with moderate-to-severe paraquat (PQ) poi- soning, and the results showed only 25% mortality rate in the pulse therapy group and 70.6% mortality in the control group (2). The dose was not the same as that used in Addo’s study (3), which used high dose of CP for 2 wk. We found that 5% of pulse therapy group patients developed leukopenia (WBC < 3,000). In addition, all of them survived. This observation, similar to a previous report (3), implies that CP-induced leukopenia may contribute to survival of PQ-poisoned patients. The mechanism is unknown and may re- sult in partially reducing inflammation of PQ poisoning (4). The dose of CP in treating these patients was about 15 mg/kg per day. Hence, we used the
dose, 15 mg/kg, of CP for 2 d in treating patients with PQ poisoning in the prospective clinical trial (1).

The dose of CP was 15 grams (g)/kg in our previous paper (1) was a typo- graphical error and should be 15 milligrams (mg)/kg. We are glad to have a chance to correct this error in our work.

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1. Lin JL, Leu ML, Liu YC, Chen GH. A prospective clinical trial of pulse ther- apy with glucocorticoid and cyclophosphamide in moderate to se- vere paraquat-poisoned patients. Am J Respir Crit Care Med 1999;159:

2. Lin JL, Wei MC, Liu YC. Pulse therapy with cyclophosphamide and methylprednisolone in patients with moderate to severe paraquat pois-


used for normative data, age 20–29, (presumably) mostly white (4) is not representative for the entire population.

VALENTIN POPOA
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From the Authors:

We thank Dr. Popa for his comments and apologize for overlooking his study. From the Authors

We acknowledge the superiority of using a clinical estimation of the pretest probability of asthma, modified by methacholine challenge results. The document clearly states that our Figure 3 was included only for illustration purposes and should not be used to calculate precise post-test probabilities in patients (5). The pretest probability of asthma in any given patient is only a rough clinical estimate, and our intention was to give a qualitative illustration of how the MCT result could alter the pretest probability estimate. We look forward to research that will allow quantitative estimates of post-test probabilities.

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ENDOGENOUS AIRWAY ACIDIFICATION: IMPLICATIONS FOR ASTHMA PATHOLOGY

To the Editor:

A recent article by Hunt and colleagues (1) reports that the pH of airway vapor condensates is relatively acidic in patients with acute asthma and returns to normal with treatment. They suggest that the pH of the exhaled vapor reflects the pH of the airway surfaces in these patients on the basis of comparisons made with undiluted tracheal secretions obtained in three patients.

Although measurements of pH of exhaled vapor may prove useful, there are a number of aspects of the study that are of some concern. The investigators passed the exhaled air through a 0.3 μm filter. The rationale for this approach is not explained, but it may have been used to remove saliva. However, if all droplets of any size were successfully removed from the exhaled air, then the samples could not contain any nonvolatile acids or buffers. The investigators collected the condensate in a cooled aluminum condensing conduit and then aerated the samples with argon. Deaeration should have removed most of the volatile acids (e.g., CO₂/H₂CO₃ and NO/HNO₃). Fluid collected in this fashion should be nearly devoid of any acids or buffers and the pH would therefore be extremely difficult to measure accurately in the pH 5–8 range. Contact with any surface (e.g., the aluminum of the conduit or the plastic or glass in the collecting vials) could have a profound effect on the pH of the collected samples. Furthermore, the presence of NO in the exhaled air could have an effect on the interaction of the collected fluid and the aluminum of the conduit. It may prove very difficult to determine what the putative acids are in the exhaled fluid, and it seems unlikely that the acids or buffers in the collected fluid are representative of those on the airway surfaces. It would be instructive to compare the osmolality of the samples (presumably close to zero) with that of the airways (nearly isotonic).

It could be argued that the droplets trapped by the filter might provide a more accurate indication of the pH of the airways than water vapor. (Was the bathwater kept and the baby discarded?) Even if some droplets of the airway fluid do make their way past the filter, the constituents of these droplets would be significantly diluted by the collected water vapor.

Richard M. Effros
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From the Authors:

We appreciate the thoughtful comments of Dr. Effros. Importantly, he suggests that water vapor may dilute particulate solutes in condensation assays. Particulates aerosolized from the airway wall may indeed seed vapor condensation. Thus, the degree of lower airway acidification in acute asthma may be greater than what we measured (1).

Dr. Effros is correct that filtration prevents salivary contamination. Our system is designed (1, 2) to collect particles less than 0.3 μm diameter (3), and boiled acids (pH 4–5) condensed through our system have little change in pH. We and others are investigating what does and does not go through filters of various sizes during condensate collection. However, lower airway particles are clearly of more immediate interest than saliva—which does not come through in our system—when it comes to studying asthma biology.

Dr. Effross correctly points out that deaeration removes CO₂; this was our objective. With the acidic CO₂ removed, the pH is remarkably stable over time and is reproducible on repeated studies of the same subject (coefficient of variation 3.3% [1]). Nitric oxide (NO) loss is trivial. It evolves rapidly
from water without deaeration (solubility \( \sim 0.05 \times \) that of \( \text{CO}_2 \) [4]), and airway concentrations are three log orders lower than \( \text{NO}_2^- \) (5), and five log orders lower than \( \text{CO}_2 \). In any case, removing \( \text{NO}_2^- \) as NO during deaeration would have the effect of alkalinizing the solution while depleting \( \text{NO}_2^- \) (6). On the contrary, the acidic (acute asthmatic) samples were depleted in \( \text{NO}_2^- \). Thus, acidification is likely the primary event leading to NO production through loss of protonated \( \text{NO}_2^- \).

Reactions in the collection device itself did not affect our results. Results were identical whether aluminum, stainless steel, tygon, cellulose acetate, or polyvinyl chloride collection systems were used (1, 2; unpublished observations). The system was fastidiously washed with deionized water (18 M\( \Omega \)-s), dried with high grade inert gas and sealed before use. Our samples were likely less reactive than soda beverages, which have the same pH (3.2–3.3) whether collected and stored in aluminum or plastic containers!

In any event, these interesting considerations do not account for the large difference in H\(^+\) concentration between lower airway particles collected from patients with acute asthma and those from controls. Nor do they explain the normalization of pH with corticosteroid therapy. These clinical differences are also not explained by expiratory flow limitation or inhaled medications (1). Indeed, we believe that there is a distinct biochemical explanation for low airway pH in acute asthma that involves the airway epithelium itself.

We agree with Dr. Effros that there is much to be learned from analysis of different fractions of expired air; and that the pH of the asthmatic lower airway may indeed be even more acidic than we can measure with noninvasive techniques. We are entering an era in which analysis of airway ion concentration will be the focus of more attention than ever before (1, 7); reasoned comparison of techniques used for sample collection will be critical.

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