ORIGINAL ARTICLE

A META-ANALYSIS OF ORAL VERSUS INTRAVENOUS *N*-ACETYLCYSTEINE THERAPY FOR PARACETAMOL POISONING

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Abstract

Objective: **Paracetamol overdose is the most common cause of drug-related poisoning and death worldwide. Although *N*-acetylcysteine is the widely accepted antidote for paracetamol poisoning, much debate persist regarding the appropriate route and duration of early *N*-acetylcysteine therapy. There is a paucity of studies comparing the effectiveness of oral and intravenous (IV) acetylcysteine for paracetamol poisoning. *Methods*: A literature search was performed using the keywords [paracetamol OR acetaminophen] AND [acetylcysteine OR n-acetylcysteine] on the PubMed and Ovid database. The literature search was limited to human exposure studies published in English between 1-Jan-1966 and 1-May-2015. The proportion of patients who developed hepatotoxicity (defined as serum transaminase greater than 1000 IU/L) for each route of administration was determined using multiple regression and the studies were further stratified by early (less than 10 hours from ingestion) and late treatment (longer than 10 hours from ingestion). *Results:* 3,981 full studies were reviewed for data. Studies with fewer than 20 subjects were excluded. Meta-analysis revealed that the overall proportion of patients who developed hepatotoxicity was 12.3% (95% confidence interval [CI]: 9.6% to 17.2%). The percentages were similar when studies were stratified by route of administration; the proportion for IV treated patients was 12.6% (95% CI: 8.7% to 19.4%) while the proportion for oral treated patients was 12.0% (95% CI: 8.2% to 18.8%). However, there was a marked difference in the percentage of patients who developed hepatotoxicity with early as compared to late *N*-acetylcysteine treatment. There was a statistically significant effect due to time ($p < 0.001$) but no significant effect due to route of administration ($p = 0.716$). *Conclusion*: Pooled analysis of studies did not find any significant difference in outcome between oral and IV *N*-acetylcysteine therapy, but these findings require confirmation by randomized controlled trials. However, overall hepatotoxicity was significantly worse if treatment was delayed beyond 8 to 10 hours. *ASEAN Journal of Psychiatry, Vol. 17 (2): July – December 2016: XX XX.***

Keywords: Paracetamol Poisoning, *N*-Acetylcysteine, Oral Administration, Intravenous, Delayed Treatment

Introduction

Patients with mental illnesses may resort to intentional overdoses for various reasons. Paracetamol can be easily purchased over-the-counter, and paracetamol overdose is thus one of the most common causes of drug-related poisoning and death worldwide [1]. Doses of paracetamol exceeding 150 mg/kg in a patient can be life-threatening.

Although *N*-acetylcysteine (a sulfhydryl group

donor) is the widely accepted antidote for paracetamol poisoning, much debate still persists regarding the appropriate route and duration of *N*-acetylcysteine therapy [2]. Traditionally, IV N-acetylcysteine has been the favoured route of drug administration in countries such as Australia, Europe, and Canada [3], while oral N-acetylcysteine has been used in the United States (US). Subsequently, an IV formulation was approved for use in 2004 and is now the most common route of administration for *N*-acetylcysteine used in the US [4].

Despite the prevalence of paracetamol poisoning, there is a paucity of studies comparing the effectiveness of oral (PO) and intravenous (IV) acetylcysteine, with no head-to-head or randomized controlled trials comparing the efficacy of these two routes. As such, the objective of this study is to systematically review the evidence supporting the use of oral and IV acetylcysteine for paracetamol poisoning. The percentage of patients who develop hepatotoxicity during treatment and the efficacy in relation to the time of drug administration for the two routes will be examined.

Methods

A literature search was performed using the keywords [paracetamol OR acetaminophen] AND [acetylcysteine OR n-acetylcysteine] on the PubMed and Ovid database. Together, this covers a wide variety of databases, including MEDLINE, PreMEDLINE, EBM (Evidence Based Medicine) Reviews, Cochrane Database of Systematic Reviews, and EMBASE (ExcerptaMedica Database, a major biomedical and pharmaceutical database well known for its international scope). The literature search was limited to human exposure and studies published in English between 1-Jan-1966 and 1-May-2015. For relevant abstracts, full articles were obtained, reviewed and checked for references of interest.

The inclusion criteria for this review were: (1) toxic paracetamol concentration defined using either the "150" or the "200" treatment line on the Rumack-Matthew Nomogram, (2) acetylcysteine treatment, with route specified, (3) biochemical measurement of AST or ALT post-treatment levels, and (4) studies with at least 20 human subjects (to decrease the bias associated with small studies).

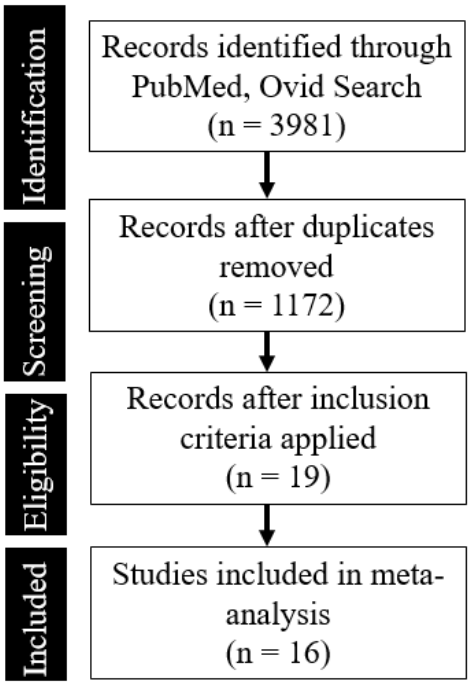

Figure 1. PRISMA diagram showing the studies identified during the literature search and abstraction process

The proportion of patients who developed hepatotoxicity (defined as serum transaminase greater than 1000 IU/L) for each route of administration was analysed using multiple regression and the studies were further stratified by early (less than 10 hours from ingestion) and late treatment (longer than 10 hours from ingestion). All analyses were done using MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014).

Results

Table 1. Characteristics of all studies included in this review (arranged alphabetically by first Author's last name)

Author, year [reference]	Sample size	Study design	Treatment threshold (mg/L)	Mean Age (years)
Buckley, 1999 [5]	981	Retrospective	150	45
Chan, 1995 [6]	224	Retrospective	200	34
Doyon, 2009 [7]	77	Retrospective	150	28.3 ± 15.7
Klein-Schwartz, 2007 [8]	28	Prospective	150	34
Parker, 1990 [9]	20	Prospective	150	36
Prescott, 1981 [10]	100	Prospective	200	33
Rumack, 1981 [11]	662	Prospective	150	29
Sivilotti, 2005 [12]	1270	Retrospective	150	22.1
Smilkstein, 1991 [13]	179	Prospective	150	21.3 ± 9.5
Smilkstein, 1988 [14]	11,195	Prospective	200	Not specified
Spiller, 1994 [15]	122	Prospective	150	22.0 ± 0.9
Spiller, 2006 [16]	145	Prospective	200	26.1 ± 12.5
Tsai, 2004 [17]	75	Prospective	150	25.6 ± 8.8
Tsai, 2005 [18]	27	Retrospective	150	26.7 ± 10.2
Whyte, 2007 [19]	1749	Retrospective	150	29.0 ± 12.9
Woo, 2000 [20]	75	Retrospective	150	Not specified
Wright, 1999 [21]	42	Retrospective	150	22 ± 10
Yarema, 2009 [22]	4048	Retrospective	150	Not specified
Yip, 2003 [23]	34	Prospective	150	Not specified

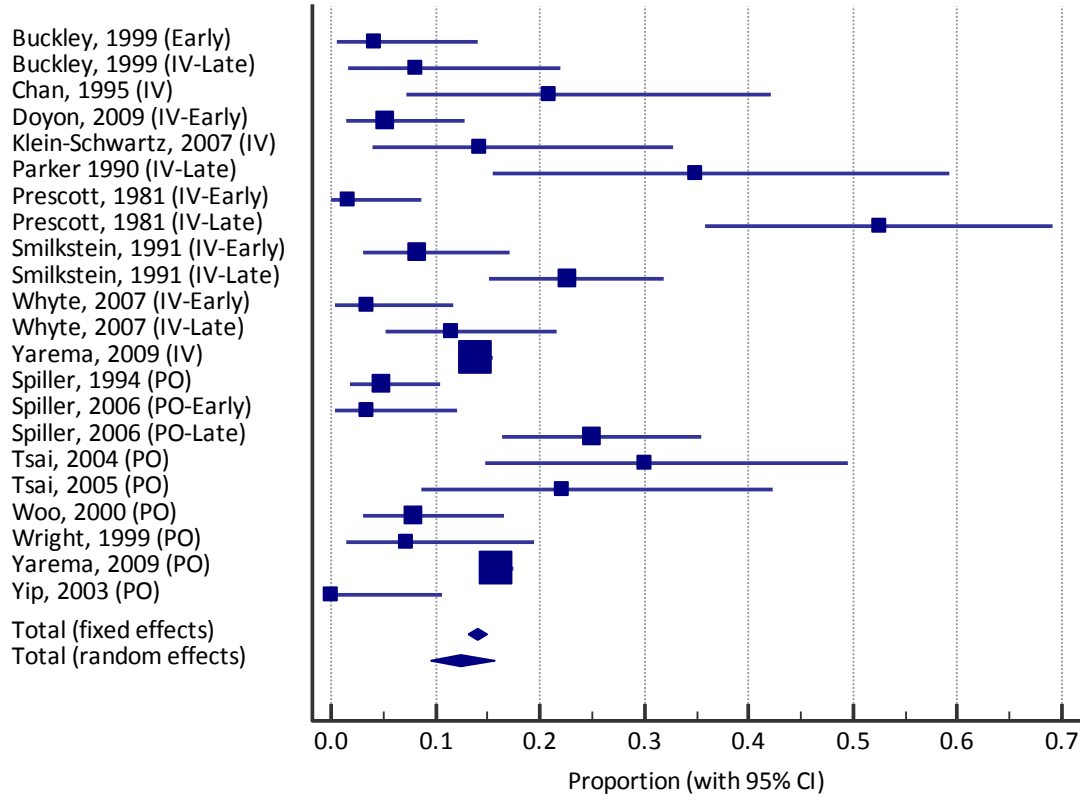

Figure 2. Forest plot showing proportion of patients who developed hepatotoxicity with either intravenous (IV) or oral (PO) acetylcysteine treatment

The overall proportion of patients who developed hepatotoxicity was 12.3% (95% CI: 9.6% to 17.2%). The percentages were similar when studies were stratified by route of administration; the proportion for IV acetylcysteine treated patients was 12.6% (95% CI: 8.7% to 19.4%) while the proportion for oral acetylcysteine treated patients was 12.0% (95% CI: 8.2% to 18.8%).

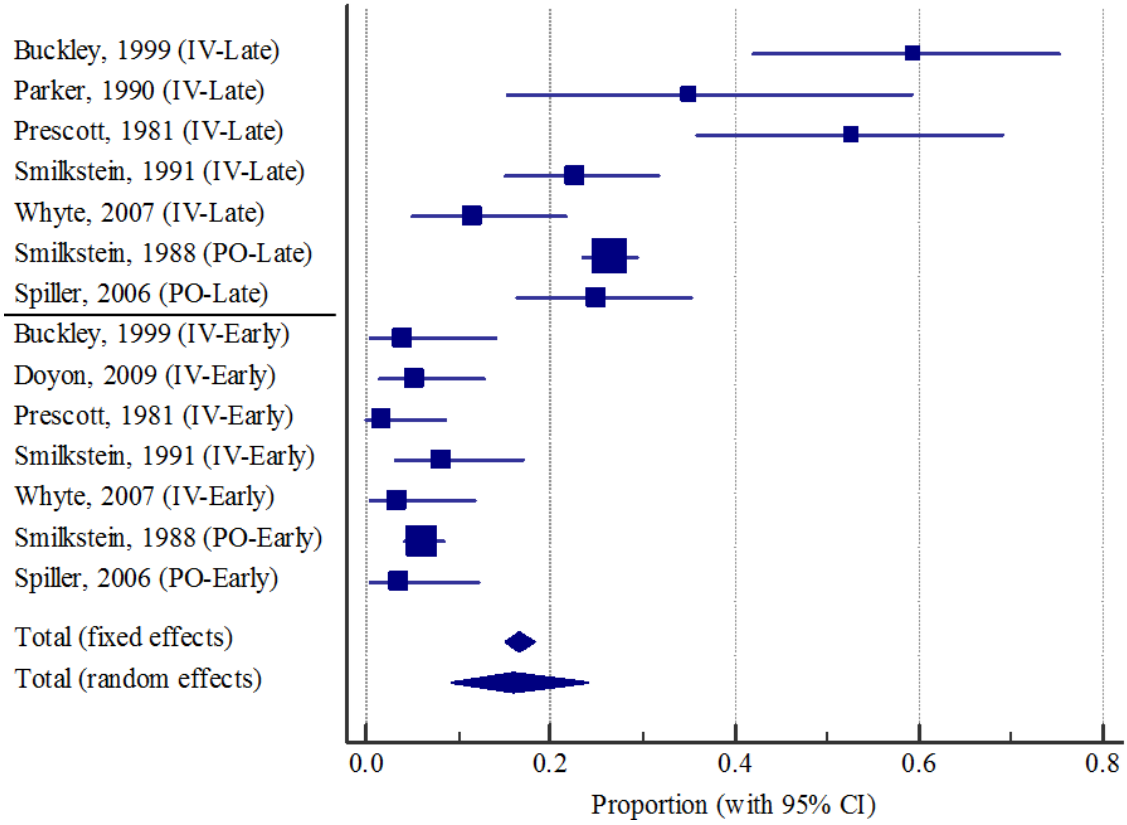

Figure 3. Forest plot showing proportion of patients who developed hepatotoxicity when intravenous and oral acetylcysteine treatment was administrated early (less than 10 hours from ingestion) and late (more than 10 hours from ingestion)

The relationship between route (IV or oral) and time (early or late) of administration was analysed using a multiple regression model. The regression analysis found no significant route by time interaction ($p=0.692$). However, there was a statistically significant effect due to time ($p<0.001$) but no significant effect due to the route of administration ($p=0.716$).

Discussion

Pooled analysis of studies did not find any significant difference in outcome between IV and oral *N*-acetylcysteine therapy, but these findings require confirmation by randomized controlled trials. However, as seen in Figure 3, overall hepatotoxicity was significantly worse if treatment was delayed beyond 8 to 10 hours.

The current evidence is not based on randomized, placebo-controlled trials and might vary across levels of patient risks, with possible confounding effect due to dose and duration of treatment, but overall suggests that if a difference exists, it is likely to be small. Without clear patient level data, several potential confounders that may be associated with outcome of paracetamol overdose such as age, pre-existing liver disease, chronic alcohol abuse, etc. cannot be accounted for.

Furthermore, in some of the studies, activated charcoal (a gastrointestinal decontamination agent) was administrated in addition to *N*-acetylcysteine therapy. This could have complicated study outcomes and it is difficult to adjust for its effects. Although it has been postulated that activated charcoal may affect the pharmacokinetics of oral *N*-acetylcysteine (via adsorption and inactivation by activated charcoal) [24], observational evidence does suggest that co-administration of *N*-acetylcysteine and activated charcoal is safe and does not decrease the efficacy of *N*-acetylcysteine or result in poorer clinical outcomes [15]. In fact, this could have improved the outcomes of treatment with acetylcysteine as recent evidence demonstrates

that administration of activated charcoal is associated with a decreased incidence of hepatotoxicity in individuals who received *N*-acetylcysteine therapy within 24 hours [25]. It is challenging to adjust for the effects of activated charcoal use without a clear understanding of its precise mechanism of action.

This study is also limited by being a single-author review, but utmost efforts have been made to ensure accuracy and fidelity of study selection, data extraction, analysis and interpretation. An extensive range of databases have also been included in the literature search process.

Given current best evidence, IV and oral *N*-acetylcysteine are both equally efficacious routes of drug administration and the following are some factors clinicians should take into account as well. In fulminant hepatic failure, only IV administration has been shown to be effective [26]. For patients with severe nausea or vomiting, delivery of oral medications may be impeded. For patients with altered mental status, oral administration increases the risk of aspiration. For patients with gastrointestinal dysfunction or bowel obstruction, oral medications may not be absorbed as effectively. Last but not least, in the case of severely atopic patients, or patients with severe asthma, or prior severe drug reaction to IV acetylcysteine, IV N-acetylcysteine should be used with great caution. Prospective studies suggest that between 10 to 20% of patients treated with IV acetylcysteine develop a hypersensitivity/anaphylactoid (non-IgE mediated) reaction [27].

Conclusion

The key to effective treatment is to start acetylcysteine therapy early (be it via the oral or IV route), before the onset of liver injury, which can be detected by an elevation of AST/ALT. Clinicians should select a suitable route of administration based on individual patient factors and institutional factors e.g. availability of drug.

Acknowledgements

No conflict of interest to disclose. Project was completed with no external funding.

The author would like to acknowledge Prof Ong Choon Nam (National University of Singapore), Dr Chan Hwei Wuen (National University Health System) and Dr Donovan Lim Yutong (Institute of Mental Health) who provided much guidance and support.

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Received: 20 June 2016 Accepted: 22 September 2016