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Hemodynamic changes in patients with influenza A after propacetamol infusion in the emergency department

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ABSTRACT

Objectives: Recently, there has been an emerging clinical data suggesting that intravenous propacetamol may cause iatrogenic hypotension. The primary objective of this study was to evaluate hemodynamic changes after propacetamol infusion in the emergency department (ED) with the patients of influenza A. Secondary objective was to assess the incidence of propacetamol-induced significant hypotension and to evaluate factors associated with this adverse effect by comparing two groups of patients with or without a significant reduction in blood pressure (BP).
Methods: We retrospectively reviewed the medical records of the patients with laboratory-confirmed influenza A who received intravenous propacetamol for the control of fever in the ED during the 2015–16 influenza season.
Results: 101 patients of influenza A were included in this study. Overall, all the vital signs including BP, pulse rate and body temperature recorded after propacetamol administration were lower than the pre-infusion values. A significant reduction in BP was observed in 30 (29.7%) patients and 6 (20%) of them required crystalloid infusion. Interestingly, pre-infusion BPs were higher in the group of propacetamol-induced significant hypotension, yet there was no difference in post-infusion BPs between the groups.
Discussion: To our knowledge this is the first study on the effect of intravenous propacetamol in the ED patients with influenza A infection. We hypothesized that the group with a significant reduction in BP could have higher sympathetic tone, consequently showing higher pre-infusion BPs and pulse rate. And there was no difference in post-infusion BPs because baroreflex homeostasis could compensate further decrease in BPs.

1. Introduction

During the 2015–16 influenza season, >665,000 specimens tested were positive for influenza virus in the United States [1]. In the absence of specific treatments for influenza, management has been focused on the relief of associated symptoms such as fever or myalgia. Guidelines recommend that antipyretic treatment with paracetamol is routinely administered to adults who develop an influenza-like illness during an epidemic or pandemic [2]. This recommendation is qualified by accumulated experience which suggests that it may help and is unlikely to be harmful [3].

Paracetamol (acetaminophen) is a selective inhibitor of cyclooxygenase-2, which has been used as an analgesic and antipyretic agent since 1950 [4]. A prodrug of paracetamol, propacetamol shows additional benefits of being water soluble and convertible by plasma esterase [5]. A 2 g dose of propacetamol yields 1 g paracetamol [6]. This intravenous (IV) formulation, propacetamol is widely used in the emergency department (ED) because it reaches peak plasma concentrations faster (15 min vs. 2 h) than oral paracetamol [7].

Recently, there has been an emerging clinical data suggesting that IV propacetamol may cause iatrogenic hypotension. Even though there has been little scientific evidence in the ED regarding this adverse effect, hypotension associated with the IV administration of propacetamol is well known to ED nurses and doctors. Therefore, in this present study, we evaluated the hemodynamic effects of IV propacetamol in ED with patients who have laboratory-confirmed influenza A infection. We evaluated hemodynamic changes after its administration and attempted to identify clinical factors related to significant reduction of blood pressure (BP) as well.

2. Methods

2.1. Study design

We retrospectively reviewed the medical records of the patients with laboratory-confirmed influenza A who received IV propacetamol for the control of fever in the ED during the 2015–16 influenza season (August 1, 2015–August 31, 2016).

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The primary objective of this study was to evaluate hemodynamic changes after administration of IV propacetamol in the ED with the patients of influenza A. Secondary objective was to assess the incidence of propacetamol-induced significant hypotension in these patients and to evaluate factors associated with this adverse effect by comparing two groups of patients, one with a significant reduction in BP after propacetamol infusion and the other without it.

2.2. Study population

This study was conducted in a university hospital in Korea which is a tertiary hospital with 54,000 patients according to an annual census of ED visits. We included normotensive febrile patients with laboratory-confirmed influenza A. Patients whose age ≥ 16 years, initial BPs were ≥120/80 mm Hg, and tympanic temperature was ≥38 °C were enrolled. Influenza A was diagnosed with a rapid influenza antigen kit; nasopharyngeal swabs were obtained using Copan Floq swabs and the presence of influenza antigens was investigated using the BD Directigen Flu A + B (Directigen; Becton-Dickinson, Sparks, MD).

Propacetamol (Denogan®, Propacetamol hydrochloride 1 g/ample, Young-Jin Medical, Korea) was infused over 30 min after mixing it with 100 mL of 5% dextrose water or normal saline. Considering the duration of infusion and a previous study by Boyle et al. who provided evidence that IV paracetamol can cause reduced BP up to 60 min [8], we included patients whose follow-up vital signs within 90 min after the order of IV propacetamol in the ED were recorded.

2.3. Data collection and outcomes

We collected data on patient demographics, comorbidities and laboratory results. Duration of fever upon arrival at the ED were grouped into three categories: duration <24 h, 24 h ≤ duration < 48 h, and duration ≥ 48 h. Dose of propacetamol and any interruption of infusion were recorded. Vital signs including systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate (PR) and body temperature (BT) were collected. We defined the vital signs at the time of ED presentation as baseline (pre-infusion) parameters. Follow-up vital signs within 90 min after the order of IV propacetamol were collected as post-infusion hemodynamic parameters. If there were more than one follow-up vital signs, the lowest values were recorded. A significant reduction in BP were defined as SBP < 90 mm Hg or DBP < 60 mm Hg, or a drop in SBP ≥ 30 mm Hg. For the patients with significant reduction in BP, additional treatments were recorded such as a fluid bolus or use of vasopressor.

2.4. Data analysis

In the preliminary analyses, summary statistics are presented as means with standard deviations or medians with interquartile ranges for continuous variables, and percentages for categorical variables. A paired *t*-test was used for comparisons of pre- and post-infusion vital signs. Categorical variables were compared using the chi-square test or Fisher exact test, as appropriate. Continuous variables were compared using the nonparametric Wilcoxon signed rank test or the Mann-Whitney *U* test. All statistical analyses were performed using MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium).

3. Results

3.1. Patient characteristics

During the study period, 101 patients of influenza A were included in this study. The baseline characteristics of the patients are shown in Table 1. 37 patients (36.6%) were men and the median age was 43.6 ± 16.3 years. 59.4% of patients visited ED within 24 h since fever had developed. Given propacetamol dose ranged from 1 g (25.7%) to 2 g (74.2%) and infusion was never interrupted. As for comorbid conditions, the percentages were <8% for each one.

Table 1
Comparison of baseline characteristics and hemodynamic parameters between patients with and without significant reduction in blood pressure.

	Total patients (n = 101)	Significant reduction in BP		p value
		No (n = 71)	Yes (n = 30)	
Age, yr	43.6 ± 16.3	43.2 ± 16.4	44.4 ± 16.3	0.741
Male sex, no. (%)	37 (36.6)	28 (39.4)	9 (30.0)	
Onset of fever, no. (%)				
<24 h	60 (59.4)	44 (61.9)	16 (26.6)	
24 h ≤ <48 h	24 (23.7)	16 (22.5)	8 (33.3)	0.420
≥48 h	17 (16.8)	11 (15.4)	6 (35.2)	
Dose of propacetamol, no. (%)				
1 g	26 (25.7)	17 (23.9)	9 (30.0)	0.526
2 g	75 (74.2)	54 (76.0)	21 (70.0)	
Comorbid conditions, no. (%)				
Hypertension	8	5	3	0.691
Diabetes mellitus	7	5	2	1.000
Heart disease	3	1	2	0.209
Respiratory disease	1	1	0	1.000
Liver disease	6	5	1	0.631
Renal disease	0	0	0	
Neurodegenerative disease	4	3	1	1.000
Hematologic disease	2	2	0	1.000
Rheumatologic disease	4	4	0	0.315
Cancer	5	3	2	0.631
Vital signs on presentation				
SBP, mm Hg	134.9 ± 20.0	124 (119–136)	148 (140–164)	<0.0001***
DBP, mm Hg	77.8 ± 10.2	76 (70–80)	86 (80–90)	<0.0001***
PR, beats/min	100.2 ± 17.1	99.0 ± 17.8	102.9 ± 15.4	0.307
RR, breaths/min	18.8 ± 1.8	18 (18–20)	18 (18–18)	0.298
Body temperature, °C	38.6 ± 0.5	38.6 (38.2–39.0)	38.7 (38.1–39.0)	0.890
Laboratory findings				
Leukocyte count, cells/mL	7518 ± 8814	6075 (4860–8140)	6700 (5565–7797)	0.519
Hemoglobin, g/dL	13.2 ± 1.9	13.3 (12.3–14.6)	13.3 (12.6–14.0)	0.617
Platelet counts, $10^3/\mu L$	184.5 ± 55.9	170.5 (146–215)	198 (160–216)	0.149
CRP, mg/dL	2.9 ± 4.1	1.88 (0.80–3.42)	1.88 (0.92–3.75)	0.872
BUN/creatinine ratio	14.1 ± 4.8	12.6 (10.7–15.1)	14.3 (10.8–17.4)	0.207
Urine specific gravity	1.021 ± 0.008	1.020 (1.014–1.025)	1.024 (1.020–1.026)	0.081

*p < 0.05, **p < 0.01 ***p < 0.001.

3.2. Hemodynamic changes after IV propacetamol

Overall, all the vital signs including BP, PR and BT recorded after propacetamol administration were lower than the pre-infusion values: SBP changed from 134.9 ± 20.0 mm Hg to 116.6 ± 14.1 mm Hg (p < 0.0001), and DBP changed from 77.8 ± 10.2 mm Hg to 72.8 ± 10.2 mm Hg (p = 0.001) after IV paracetamol. The PR following propacetamol injection decreased from 100.2 ± 17.1 beats/min to 88.1 ± 12.8 beats/min, and BT improved from 38.6 ± 0.5 °C to 38.0 ± 0.5 °C (p < 0.0001).

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