Outcome of Paracetamol Poisoning After Treatment With Intravenous or Oral N-acetylcysteine

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ABSTRACT

Introduction: Paracetamol (PCM) is one of the commonest drug in clinical practice and it is generally safe for use at recommended doses. However, its overdose can cause mild hepatotoxicity to severe hepatic necrosis and even hepatic failure. N-acetylcysteine (NAC) is the standard recommended antidote for PCM poisoning which is available in both intravenous (IV) and oral formulations. This study aimed to measure outcome in PCM poisoning after treatment with oral or IV NAC.

Methods: A descriptive cross-sectional study was conducted in randomly selected 50 consecutive patients presented within 72 hours of PCM poisoning. Comparative outcomes were measured in correlation of dynamics of liver enzymes alanine aminotransferase, aspartate aminotransferase and prothrombin time along with development of adverse drug reactions and clinical cure rate. Comparison of categorical variables by Chi-square test and Fisher's test were done and the comparison of mean between groups by Student's t-test with p-value <0.05 as statistically significant.

Results: Among 50 cases 20 (40%) were treated with oral NAC and 30 (60%) with IV NAC. PCM poisoning was more common in young adults (15-30 years) with mean age of 19 (n=43; 86%) and most of them had taken with an intent of suicide (n=47; 94%). Majority of patients were asymptomatic at presentation with female preponderance (M:F=1:4; 80%). There was no statistical difference in both the treatment groups and as an outcome measure there were no severe liver enzymes derangement, no serious adverse drug reactions and 100% clinical cure rate.

Conclusion: NAC in both IV and oral forms are equally effective as an antidote in PCM poisoning.

Keywords: outcome; paracetamol poisoning; hepatotoxicity; N-acetylcysteine; intravenous; oral

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INTRODUCTION

Paracetamol (PCM, Acetaminophen) is one of the most widely used drug in the world. It is an effective mild analgesic, antipyretic agent which is inexpensive and mostly sold as an over the counter drug. It is generally safe for use at recommended doses (1000 mg per single dose and up to 4000 mg/day for adults and 2000 mg/day for alcoholics).[1,2] PCM poisoning occurs mostly because of suicidal tendencies and less commonly accidental. It is a major public health problem in the Western world mainly Europe and United States of America.[3] However this is becoming one of the public health problem in our country as well especially among youngsters in urban areas.[4]

PCM has a narrow therapeutic index and the therapeutic dose is close to the toxic dose. To cause toxicity, an acute overdose must total be more than or equal to 150 mg/kg (about 7.5 gram in adults) within 24 hours.[5,6] Its overdose can cause mild hepatotoxicity to severe hepatic centrilobular necrosis and even liver failure. However, mostly the catastrophic outcomes and liver related deaths are uncommon who present to the hospital within 16 hrs of ingestion.[7] Though mechanism of PCM induced liver injury is still not completely understood, in the initial phases of toxicity PCM is metabolically activated by cytochrome P450 enzymes to a reactive intermediate metabolite, N-acetyl-p- benzoquinoneimine (NAPQI) that depletes glutathione (GSH) and covalently bind to cellular proteins including mitochondrial proteins.[8]

The estimated serum PCM concentration in relation to the post ingestion time is interpreted using the nomogram. The standard nomogram recommends estimation of serum PCM level every four hours, which is plotted in a graph. This guides for general line of management whether the case falls within standard treatment line or high risk treatment line and it also provides clinicians a method to predict whether patients would develop hepatic toxicity following an initial serum level after an overdose of PCM.[9]

N- acetylcysteine (NAC) is the standard recommended antidote for PCM poisoning that acts by repletion of GSH. It is available in both oral and intravenous (IV) forms.[10] The IV formulation has been available in Europe for over 30 years but introduced in USA only in early 2004, where oral formulation was the only Food and Drug Administration (FDA) approved antidote earlier. Since then debate of superiority of oral and IV NAC started and numerous researches carried out and still going on to the subject.[5,11]

The approved therapeutic duration for oral NAC is 72 hours (140 mg/kg body weight stat followed by 17 doses of 70 mg/kg every 4 hours with a total dose of 1330 mg/kg over 72 hours) and IV NAC is 20 hours (150 mg/kg in 200 ml of 5% Dextrose over 15 minutes followed by 50 mg/kg in 500 ml of 5% Dextrose over next 4 hours and then 100 mg/kg in one liter of 5% Dextrose over next 16 hours with a total dose of 300 mg/kg given over 20 hours).[7,12] Available formulations of NAC in our market, (Tablet NACFIL 600 mg: Fourt's India Ltd, Tamil Nadu, India; Injection Mucomix 20%: Samarth Life Sciences Pvt Ltd, Himanchal Pradesh, India).

Many researches have shown that both formulations are equally effective and some comparative studies have even shown that oral forms have better outcomes in those who present late for treatment in hospitals.[13,14]

The facilities of toxicological analysis are not commonly available in most hospitals of developing countries including Nepal. Regarding PCM poisoning there is no specific data available

Table 1: Dynamics of liver enzymes (ALT, AST) and prothrombin time (PT) over seven days in PCM poisoning cases treated with oral and IV NAC. **P:** P value.

Variables and unit	Days											
	Day1			Day3			Day5			Day7		
	Oral	IV	P	Oral	IV	P	Oral	IV	P	Oral	IV	P
	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
ALT, U/L												
30-50	10	15	0.92	2	7	0.59	12	13	0.89	5	7	0.62
51-100	8	11		14	18		4	6		4	5	
101-200	2	4		4	5		2	2		9	12	
mean ± SD	54.45± 22.5	57.93± 25.22	0.60	73.40± 23.29	61.85± 25.03	0.28	53.55± 27.45	52.14± 21.90	0.86	53.11± 15.55	48.33± 17.78	0.52
AST, U/L												
30-50	12	17	0.95	6	15	0.37	15	18	1.00	8	11	1.00
50-100	7	11		11	12		3	3		1	1	
101-200	1	2		3	3							
mean ± SD	46.85± 24.50	48.50± 17.63	0.73	61.85± 23.60	55.03± 21.82	0.30	41.22± 9.68	40.90± 8.17	0.91	41.22± 9.68	39.66± 5.88	0.30
PT, sec												
12-20	19	29	1.00	18	28	1.00	18	21	1.00	9	12	-
21-30	1	1		2	2							
Mean ± SD	14.40± 2.25	14.40± 2.25	1.00	14.90± 3.11	14.93± 2.72	0.96	13.61± 1.24	13.52± 1.28	0.83	13.44± 1.01	13.50± 1.08	0.90

and there is no separate study as such till date in our country.[15]

Our aim in this study was to measure outcome of PCM poisoning after treatment with oral or IV NAC in correlation with dynamics of liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST) and prothrombin time (PT), development of adverse drug reactions and clinical cure rate amongst those who presented in hospital within 72 hours of poisoning.

METHODS

This study was conducted after ethical approval from Institutional Review Board (IRB) and Department of Medicine-NAMS. Patients were enrolled after written informed consent was obtained. A descriptive cross-sectional study was conducted in 50 consecutive patients in tertiary care hospitals with a working hypothesis of oral and IV NAC are equally effective in PCM poisoning.

Adult patients more than 15 years of age with PCM dose of more than seven gram (>125 mg/kg body weight) presented within 72 hours of ingestion were included and anyone with pregnancy and known allergy to NAC were excluded from the study. As for any other clinical case, detail history taken from the patient and relatives as necessary. Any eye witness enquired and information

regarding apparent cause of ingestion, type of formulation, approximate dose taken, time of intake, time of arrival in the hospital and any treatments taken in between before coming to the referral center were noted. Symptoms and signs were noted and sample medicine tablets/packs were asked whenever feasible. Treatment options of either oral or IV NAC selected randomly.

Serum PCM level estimated by High Performance Liquid Chromatography (HPLC) method with therapeutic range of 10-20 mcg/ml after four hours of ingestion and before discharge from the hospital. Here the standard recommended nomogram in the treatment of PCM poisoning could not be followed because of selective laboratory facility and financial constraints. Liver enzymes ALT, AST and PT estimated daily. Clinical cases were categorized as early presenters and late presenters. Here we define early presenters as those who presented within eight hours of PCM ingestion and late presenters as those who presented after eight hours of ingestion. The comparative outcome measured in the form of dynamics of liver enzymes ALT, AST and PT, development of adverse drug reactions and clinical cure rate.

Collected data were analyzed using Statistical Package for Social Sciences (SPSS) version 19 by Microsoft corporation. The frequency and descriptive statistics were evaluated. Comparison of categorical variables was done by chi-square test and Fisher's exact test whenever appropriate and the comparison of mean between groups was carried out by Student's t-test. P value less than 0.05 was considered statistically significant.

RESULTS

Out of 50 cases 20 (40%) were treated with oral NAC and 30 (60%) with IV NAC. PCM poisoning was more common in young adults (15-30 years) with mean age of 19 (n=43; 86%) and most of them had taken with an intent of suicide (n=47; 94%). Majority of patients were asymptomatic at presentation with female preponderance (M:F=1:4; 80%) and most were unmarried (n=46; 92%) and were students (n=41; 82%).

As an outcome measure there were no severe liver enzymes derangement (Table 1), no serious adverse drug reactions (Table 2), no statistical difference in early and late presenters in both the treatment groups (Table 3) with 100% cure rate without any mortality in both oral and IV NAC groups.

DISCUSSION

In our study amount of PCM consumed was minimum of 8 gms & maximum of 42 gms with mean ± SD (19.90 ± 4.67 oral NAC ; 19.16 ± 8.48 IV NAC) and time of arrival in hospital was minimum within an hour & maximum after 23 hours with mean±SD (8.40 ± 6.26 oral NAC ; 8.80 ± 7.09 IV NAC) with altogether 45% late presenters. Most patients were asymptomatic at presentation and clinically stable. It is supported by the study done by Meredith et al[16] where mostly there were no signs and symptoms in PCM poisoning initially.

In this study maximum mean of ALT and AST was 150 U/L and 65 U/L respectively with peak level at day two with gradual decline with treatment and reversal within normal range in day five in average. Similar findings in late presenters as well. Liver is the major target organ in PCM poisoning and it is reflected by increased liver enzymes as shown by studies by Mitchell et. al.[17] and Prescott.[6] In the study by Smith et. al.,[18] only a small minority of patients were at risk of severe liver damage in PCM poisoning and even if severe damaged occursed recovery is rapid and complete. Similarly as per study by Rumach et. al.[19] PCM poisoning can result in fulminant hepatic failure and thereby death but these outcomes are uncommon.

Table 2: Adverse drug reactions in patients treated by oral and IV NAC.

Adverse Drug Reactions	Oral NAC (n=20)	IV NAC (n=30)	P Value
Anaphylactoid reaction	0	2 (7%)	
Nausea-Vomiting	4 (20%)	5 (17%)	0.73
None	16	23	

Table 3: Statistics of oral and IV NAC among late presenters. (more than 8 hours)

	Time	Oral NAC (n=9)	IV NAC (n=13)	P-value
Mean Paracetamol concentration mg/dl (mean ± SD)	Arrival	49.66 ± 22.23	46.38 ± 27.53	0.73
	Discharge	0.22 ± 0.66	0.46 ± 0.87	0.48
Liver enzymes ALT U/L (mean ± SD)	Day 1	65.00 ± 28.06	65.61 ± 28.69	0.96
	Day 4	52.77 ± 14.33	53.33 ± 13.16	0.94
	Day 8	42.50 ± 0.70	32.33 ± 0.57	0.004
Liver enzymes AST U/L (mean ± SD)	Day 1	53.11 ± 20.66	57.46 ± 22.12	0.64
	Day 4	49.65 ± 12.54	46.92 ± 12.24	0.61
	Day 8	33.00 ± 6.41	41.33 ± 6.35	0.14
Complications Nausea-vomiting, n (mean ± SD)		1	4	0.36
Duration of hospital stay, days (mean ± SD)		5.66 ± 1.41	5.84 ±1.46	0.77

In this study adverse drug reactions like nausea and vomiting were found common in both groups, total 4/20 (20%) in oral and 5/30 (17%) in IV group without any statistical significance. In late presenters more nausea and vomiting noted in IV group than oral (4:1) contrary to other studies could be due to sample bias, premedication to induce vomiting or delay absorption or associated with other medical conditions like acid-peptic disorders which are more prevalent in our part of the world. As per study by Rumach and Peterson,[19] nausea and vomiting were common manifestations after oral than IV NAC. Additionally, anaphylactoid reactions occurred in 2/30 (7%) cases in IV NAC group but none in oral group supported by Dawson et. al.,[20] stating anaphylactoid reactions like itching and urticarial rashes were common in IV NAC group.

In comparative evaluation among Oral & IV NAC groups in this study both have shown equal response and outcome without any statistical significance (P>0.05) among early & late presenters. In the study done by Lavonas et. al.,[13] oral and IV NAC were equally effective and acceptable in PCM poisoning. Similar findings with Kanter,[5] Perry,[21] and Prescott.[22-24] Moreover, in the studies done by Smilkstein et. al.[14] and Martin et. al.,[25] oral NAC appeared to be more effective than IV.

Our study had some limitations. Firstly, the sample size may be small to make any conclusion. Secondly, we may be at the tip of the iceberg with bulk of the cases not coming to our notice. Thirdly,

failure to follow the standard nomogram of serum PCM estimation may mask the exact toxicity level and there may be an error in data records. However, the study results are similar with the previous research findings and as a clinical outcome measure there was 100% cure rate without any serious adverse effects and mortality in both oral and IV NAC groups.

CONCLUSIONS

The regimens in current use for PCM poisoning are chosen arbitrarily. Several studies have shown that antidote NAC in both oral and IV forms are equally effective. Moreover some showing oral NAC is better in late presenters. Our study has also shown both oral and IV NAC have equal effect in the clinical outcome of PCM poisoning and oral NAC is not inferior to IV NAC. In a resource limited settings like ours oral NAC is fairly a good option for the treatment of PCM poisoning cases. However, it is better to individualize the treatment regimen.

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