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INJECTION SITE REACTION TO REPEATED INTRAVENOUS BOLUS INJECTION OF DICLOFENAC SODIUM IN TAIL VEIN OF WISTAR RAT

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ABSTRACT: Diclofenac is the most popular and widely prescribed non-steroidal anti-inflammatory drug (NSAID). However, no preclinical data are available on repeated diclofenac IV bolus injection. In the present study, forty male Wistar rats were randomly divided in in total of four groups with 10 rats in each group. The control group received 0.9% sodium chloride injection. Marketed injectable Diclofenac Sodium formulations of Jonac AQ (75 mg/mL), Dynapar AQ (75 mg/mL) and Voveran (75 mg/mL) were administered in group 2, 3 and 4 respectively @ 15.4 mg/kg body weight as IV bolus injection daily for seven days in the lateral tail vein. At the end of seven days treatment period, six animals per group were sacrificed. The remaining four animals per group were sacrificed after seven days recovery period. On day 8 of the study, 9/10 rats in the Voveran group, 10/10 rats in the Dynapar AQ group and 6/10 rats in Jonac AQ group showed an injection site reaction. On day 15 (reversal necropsy) of the study, 4/4 rats in Voveran group, 4/4 rats in the Dynapar AQ group and 3/4 rats in Jonac AQ group showed injection site reaction. Microscopically, intravenous injection of Jonac AQ, Dynapar AQ and Voveran induced necrosis of tail skin, thrombosis and/or thrombophlebitis, degeneration/regeneration of skeletal muscles and subcutaneous fibrosis of variable severity. In conclusion, macroscopically and microscopically, among all three marketed Diclofenac Sodium injections, Voveran group caused more severe local reaction followed by the Dynapar AQ group while Jonac AQ injection was better tolerated and revealed less severe reaction at the local injection site.

INTRODUCTION: Pain, multi-dimensional phenomenon, is an unpleasant sensation can be caused by stimulation of pain receptors located in (but not limited to) skin, joints and many internal organs [1]. Among the various type of pain, acute pain can occur secondary to acute disease processes, trauma, or operative procedures.

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In past opioid analgesics were frequently used to manage postoperative pain but were associated with a high incidence of nausea, vomiting, constipation, oversedation and respiratory depression [2]. In recent decades, non-steroidal anti-inflammatory drugs (NSAIDs) are preferred therapeutic agents used for treatment of acute pain.

Over 30 million people across the globe use NSAIDs daily for the management of pain [3]. NSAIDs are the most commonly prescribed classes of medication that have proven efficacy in managing pain, fever, and inflammation [4]. Intramuscular or intravenous NSAIDs are frequently used when oral medications is not

feasible or require rapid onset of analgesia. According to one recent survey, Diclofenac is the most popular and widely prescribed NSAID, with a market share almost equal to the combined sale of ibuprofen, mefenamic acid, naproxen [5]. Like other NSAIDs, Diclofenac inhibits cyclooxygenase enzyme hence produced a dose-dependent adverse effect on gastrointestinal, cardiovascular, and renal system [6]. Currently available parenteral formulations of diclofenac in India, have to be administered by either intramuscular injection or slow intravenous infusion [7]. In one recent study, diclofenac 75 mg/1mL, IV bolus was compared with diclofenac 75 mg / 3 mL slow IV infusion in patients with postoperative pain [7]. As per aforesaid study, diclofenac 75 mg / 1 mL, IV bolus had rapid onset of analgesia and better tolerability at injection site, however, after 12 of injection, 21.7% patients (38/175) in diclofenac 75 mg/1mL, IV bolus group, and 51.4% patients (90/175) in diclofenac 75 mg / 3 mL slow IV infusion group developed thrombophlebitis of various severity at the site of injection. In many post postoperative procedures, multiple injection of NSAIDs are required as IV bolus; however no preclinical safety data are available on repeated diclofenac IV bolus injection. Therefore, looking to the paucity of information on repeated diclofenac IV bolus injection in rats, the present study was planned in Wistar rats, to assess the local effects at the site of injection upon repeated IV bolus injection.

MATERIALS AND METHODS: Commercially available diclofenac sodium injection formulations of three different company namely 1) Injection Jonac AQ (75 mg diclofenac sodium/mL, Zydus Healthcare Ltd., Batch No. CBU1257); 2) Injection Dynapar AQ (75 mg Diclofenac Sodium/mL, Troikaa Pharmaceutical Ltd, Batch No. D23S170); 3) Injection Voveran (75 mg Diclofenac Sodium/mL, Novartis India Ltd, Batch no. 176052SP) were procured from local market.

A total of 40 male Wistar rats were procured from Cadila Pharmaceuticals Limited, Dholaka, Gujarat, India and were maintained under standard managed conditions. Rats were acclimatized for seven days before the onset of the study. For feeding, conventional standard laboratory diets were used with the *ad libitum* supply of drinking water via an automatic watering bottle. Animal care, housing and environmental conditions (temperature, humidity and light-dark cycle) were, according to recommendations stated in the Guide for Care and Use of Laboratory Animals. The experiment protocol was approved by the Institutional Animal Ethics Committee (VETCOLL /IAEC/2019/14/ PROTOCOL-03). Rats were identified by tail markings. Forty male rats were randomly divided on the basis of body weight into a total of four groups with 10 rats in each group. The control group received 0.9% sodium chloride injection. Injections Jonac AQ, Dynapar AQ, and Voveran were administered in group 2, 3 and 4, respectively @ 15.4 mg/kg body weight in the lateral tail vein (2X of the maximum recommended human dose of 75 mg/day based on mg/m^2 body surface area comparison). All four group rats were dosed intravenous (IV) bolus, daily once, for consecutive seven days with their respective test articles. Dose-volume was calculated on the basis of body weight taken on 1st day of study and were continued for 7 days. Rats were restrained in intravenous restrainers at the time of dosing. The lateral tail vein was used for dose administration and the tail vein was made prominent/raised, by applying cotton soaked in warm water.

For accurate IV injection, hyperemia of the lateral tail vein was induced by applying cotton soaked in warm water. The doses were administered by intravenous route using a suitable needle fitted with a graduated syringe. At the end of seven days treatment period, six animals per group were sacrificed. Remaining four animals per group were kept for a further seven days recovery period to see the reversibility or persistence of injection site reactions if any.

Treated animals were observed daily for mortality, clinical signs at the injection site. On day 8th (6 rats/group) and Day 15th (4 rats/group) of the study, fasted rats were sacrificed and a detailed gross examination of carcass followed by necropsy was performed. Tails of all animals were collected and preserved in 10% neutral buffered formalin. The distal, middle and proximal part of tails were trimmed transversely. Formalin-fixed samples were decalcified in formic acid before processing for routine histopathological examination. Sections of 5µ thickness were cut and stained with

Hematoxylin and Eosin method and observed under a light microscope.

RESULTS AND DISCUSSION: In comparison to animals treated with normal saline, macules were noted at the injection site after first injection in all three groups. Severity of clinical signs at injection site was increased with study advancement. In the present study, grossly assessed injection site reaction score on study day 8th and 15th are presented in **Tables 1** and **2** respectively. Gross lesions of study day 8th and 15th are presented in **Fig. 1** and **2** respectively. On day 8 of the study, two rats of normal saline group showed only focal macule of minimal severity, while rats of Jonac AQ, Dynapar AQ and Voveran showed mild to a severe reaction at the injection site. Local reactions at injection site include macule, necrosis/ulceration, dry gangrene and sloughing of the tail.

TABLE 1: LOCAL INJECTION SITE REACTION SCORE ON STUDY DAY 8TH

Group no.	Animal ID	Local injection site reaction score			
		Macule	Necrosis/Ulceration	Dry Gangrene	Sloughing of tail
0.9 % w/v Normal Saline (0 mg/kg)	1	0	0	0	0
	2	1	0	0	0
	3	0	0	0	0
	4	0	0	0	0
	5	0	0	0	0
	6	1	0	0	0
	7	0	0	0	0
	8	0	0	0	0
	9	0	0	0	0
	10	0	0	0	0
	Total	2	0	0	0
	Grand Total		2		
Jonac AQ	1	0	0	0	0
	2	1	0	0	0
	3	2	1	0	0
	4	2	1	0	0
	5	2	1	0	0
	6	0	0	0	0
	7	1	2	0	0
	8	0	0	0	0
	9	1	1	0	0
	10	1	1	0	0
	Total	10	7	0	0
	Grand Total		17		
Dynapar AQ	1	2	2	1	1
	2	1	1	0	0
	3	1	1	0	0
	4	2	1	1	1
	5	2	2	2	0
	6	2	1	2	0
	7	2	2	0	0
	8	2	2	0	0
	9	2	2	0	0
	10	2	1	0	0
	Total	18	15	6	2
	Grand Total		41		
Injection Voveran,	1	2	1	2	2
	2	2	2	0	0
	3	2	0	1	2
	4	1	0	1	2
	5	2	0	2	0
	6	2	0	0	0
	7	2	1	0	2
	8	2	1	0	2
	9	1	1	0	0
	10	2	2	0	2
	Total	18	8	6	12
	Grand Total		44		

Score description: 0 – Not found; 1 – Minimal to mild (less than 2 cm area); 2 – Moderate to severe (more than 2 cm area)

On day 8th of the study, 6/10 rats of Voveran group showed sloughing of the variable part of tail, 4/10 showed dry gangrene, 6/10 showed necrosis/ ulceration, while 10/10 rats showed variable degree macule at the injection site. In the Dynapar AQ group, 2/10 rats showed sloughing of the variable part of the tail, 4/10 showed dry gangrene, while 10/10 rats showed variable degree macule and necrosis/ ulceration at the injection site. In Jonac AQ group, 6/10 rats showed necrosis/ulceration at the injection site, while 7/10 rats showed a variable degree macule at the injection site. On day 15 of the study, reversal animals of the normal saline group did not show any local injection site reaction while reversal animals of Jonac AQ, Dynapar AQ and Voveran group showed local reactions of variable severity at the injection site. On day 15, 3/4 rats of Voveran group showed sloughing of the variable part of the tail along with other changes like necrosis/ ulceration, while 1/4 rats of Dynapar group showed sloughed tail along with other changes like necrosis/ulceration. In Jonac group 3/4 showed variable degree macule and necrosis /ulceration at the injection site. Among all three groups, Voveran group showed a more severe lesion followed by Dynapar AQ group while Jonac AQ group showed the least severe reaction among all three.

TABLE 2: LOCAL INJECTION SITE REACTION SCORE ON STUDY DAY 15TH

Group No.	Animal ID	Local injection site reaction score			
		Macule	Necrosis /Ulceration	Dry Gangrene	Sloughing of tail
Normal Saline	7	0	0	0	0
	8	0	0	0	0
	9	0	0	0	0
	10	0	0	0	0
	Total	0	0	0	0
	Grand Total			0	
Injection Jonac	7	1	1	0	0
	8	0	0	0	0
	9	1	1	0	0
	10	1	1	0	1
	Total	3	3	0	1
	Grand Total			7	
Injection Dynapar Troikaa Pharmaceutical limited	7	2	2	0	2
	8	2	2	0	0
	9	2	2	0	0
	10	1	1	0	0
	Total	7	7	0	2
	Grand Total			16	
Injection Voveran, Novartis India Ltd	7	1	1	0	2
	8	1	1	0	2
	9	1	2	0	0
	10	2	2	0	2
	Total	5	6	0	6
	Grand Total	17			

Score description: 0 – Not found; 1 – Minimal to mild (less than 2 cm area) ; 2 – Moderate to severe (more than 2 cm area)

FIG. 1: STUDY DAY 8. OUT OF SIX RAT/GROUP, ONLY FOUR RATS SHOWING MORE SEVERE LESIONS ARE INCLUDED IN IMAGES. VOVERAN GROUP SHOWED MORE SEVERE LESION FOLLOWED BY DYNAPAR AQ GROUP WHILE JONAC AQ GROUP SHOWED LEAST SEVERE REACTION AMONG ALL THREE

FIG. 2: STUDY DAY 15. VOVERAN GROUP SHOWED MORE SEVERE LESION FOLLOWED BY DYNAPAR AQ GROUP WHILE JONAC AQ GROUP SHOWED LEAST SEVERE REACTION AMONG ALL THREE

The summary of the histopathology score is presented in **Table 3**. Microscopically, in the Normal Saline group, 4/10 rats showed minimal hemorrhages around the lateral tail veins, and 2/10 showed minimal perivascular inflammation characterized by minimal to mild exudation of fibrine, infiltration of inflammatory cells and minimal edema. A 1/10 rat showed focal fibrinoid necrosis of minimal severity. In the present study, rats of Voveran (6/10 rats), Dynapar AQ (3/10) and Jonac AQ (1/10 rats) groups showed sloughing of necrotic tails on day 8. A sloughed portion of tails was not sampled for histopathology hence, clinical signs and gross pathology severity are not completely correlated with microscopic changes. Intravenous injection of Jonac AQ, Dynapar AQ and Voveran induced necrosis of tail skin, thrombosis and/or thrombophlebitis, degeneration/regeneration of skeletal muscles and subcutaneous fibrosis of variable severity.

Necrosis of tail skin was characterized by necrosis of epidermis, dermis and/or hypodermis along with infiltration of polymorphonuclear cells. In many animals of treatment group epidermis near to necrosis showed reactive hyperplasia and hyperkeratosis/parakeratosis. When compared with Normal Saline, Dynapar AQ **Fig. 3.3A** and Voveran **Fig. 3.4A** group showed high incidence and/or severity of necrosis of tail skin while Jonac AQ **Fig. 3.2A** showed a low incidence and severity of skin necrosis at the injection site. In the present study necrosis/regeneration of skeletal muscles were taken together because of the presence of both types of the lesion in the same site. Necrosis was characterized by hyalinization of muscle fibers, loss of cross striations, edema, fragmentation and loss of muscle fibers. Regeneration of skeletal muscles was characterized by the proliferation of myoblasts, presence of cells with vesicular nuclei and prominent nucleoli, and one or more centrally placed nuclei in newly regenerated muscle fibers. Variable degree of fibrosis and infiltration of inflammatory cells were noted around nearby tendons. Necrosis/ regeneration of skeletal muscles was noted in all ten rats of Dynapar AQ **Fig. 3.3B** and Voveran **Fig. 3.4B** group while 7/10 rats of Jonac AQ group (Fig. 3.2B) showed this lesion.

Thrombophlebitis was characterized by the presence of thrombus in lumen of blood vessels along with fibrinoid necrosis of blood vessels walls and /or infiltration of inflammatory cells. Thrombus/ thrombophlebitis was recorded in all ten rats of Dynapar AQ **Fig. 3.3C** and Voveran **Fig. 3.4C** group while 6/10 rats of Jonac AQ group **Fig. 3. 2C** showed these lesions. Perivascular inflammation was characterized by variable exudation of fibrine, infiltration of inflammatory cells, variable edema and minimal collagen deposition around blood vessels. Perivascular inflammations were noted in all ten rats of Dynapar AQ and Voveran group while 4/10 rats of Jonac AQ group showed this lesion.

Subcutaneous fibrosis was characterized by the proliferation of myofibroblast/fibroblast just beneath the hypodermis along with the variable deposition of collagen. Collagen deposition was more severe in recovery animals as compared to the main group. All 10/10 rats of Voveran group, 9/10 rats of Dyanapar AQ group and 7/10 rats from Jonac AQ grouped showed such lesion. Microscopically, Voveran and Dynapar AQ group showed a more severe lesion than Jonac AQ group.

TABLE 3: SUMMARY OF HISTOPATHOLOGY SCORE OF TAIL (INJECTION SITE REACTION SCORE)

Group	Severity	Group 1 Normal Saline	Group 2 Jonac AQ	Group 3 Dynapar AQ	Group 4 Voveran
Hemorrhages	WINL	6	9	10	10
	Minimal	4	1	0	0
	Severe	0	0	0	0
Fibrinoid necrosis	WINL	9	0	0	0
	Minimal	1	0	0	0
Perivascular inflammation	WINL	8	6	0	0
	Minimal	2	4	8	3
	Mild	0	0	2	7
Necrosis, Skin	WINL	0	5	0	3
	Minimal	0	1	1	3
	Mild	0	2	8	0
	Moderate	0	2	1	3
	Severe	0	0	0	1
Thrombus/ Thrombophlebitis	WINL	0	4	0	0
	Minimal	0	6	9	10
	Mild	0	0	1	0
Necrosis/Regeneration Skeletal muscles	WINL	0	3	0	0
	Minimal	0	4	8	5
	Mild	0	2	2	3
	Moderate	0	1	0	2
Subcutaneous fibrosis	WINL	0	4	1	0
	Minimal	0	3	6	7
	Mild	0	1	3	2
	Moderate	0	2	0	1

Abbreviation: NS – Normal Saline; WINL – Within normal limit

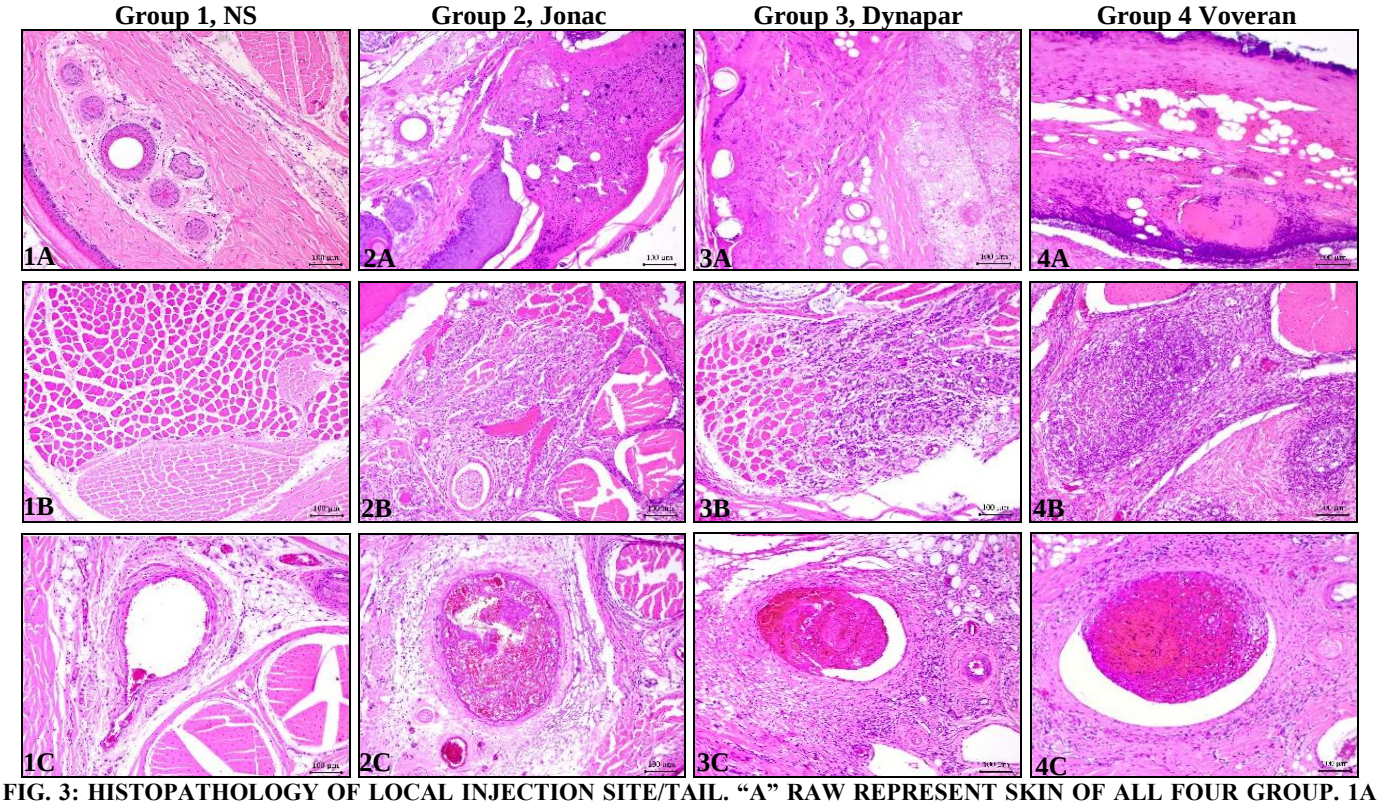

FIG. 3: HISTOPATHOLOGY OF LOCAL INJECTION SITE/TAIL. "A" RAW REPRESENT SKIN OF ALL FOUR GROUP. 1A SHOWING SKIN FROM CONTROL RAT. JONAC GROUP (2A) SHOWING MILD TAIL SKIN NECROSIS WITH REACTIVE HYPERPLASIA AT EDGES OF THE NECROSIS. DYNAPAR (3A) AND VOVERAN (4A) GROUP SHOWING MORE SEVERE SKIN NECROSIS. "B" RAW REPRESENTS SKELETAL MUSCLES AND TENDON OF ALL FOUR GROUP. IN COMPARISON TO JONAC (2B) AND DYNAPAR (3B) GROUP, VOVERAN (4B) GROUP SHOWING MORE SEVERE NECROSIS OF SKELETAL MUSCLES ALONG WITH INFILTRATION OF INFLAMMATORY CELLS. "C" RAW REPRESENTS BLOOD VESSELS AND PERIVASCULAR TISSUE OF ALL FOUR GROUP. IN COMPARISON TO CONTROL, ALL THREE GROUP SHOWING THROMBOSIS HOWEVER DYNAPAR (3C) GROUP AND VOVERAN (4C) GROUP SHOWING MORE SEVERE PERIVASCULAR INFLAMMATION THAN JONAC (2C). H&E X 100

For the treatment of acute pain, diclofenac can be administered by oral, intramuscular or intravenous routes. However, 55% of orally dosed diclofenac did not reach the systemic circulation due to first-pass metabolism [8]. While in the case of intramuscular injection, almost 30 min are required for peak plasma concentration hence the analgesic effect is a delay, as well as intramuscular diclofenac injection, which is painful [9]. Due to delayed analgesic effect in oral and intramuscular route, intravenous route of diclofenac was investigated in past studies. In clinical trials, an intravenous bolus injection of diclofenac produced a significantly faster onset of analgesia as compared to intravenous infusion of diclofenac [7]. However, intravenous bolus and infusion of diclofenac produced thrombophlebitis of various severities at the site of injection. Pain around the injection site soon after injection, erythema, livedoid patch, hemorrhagic patch and finally necrosis of skin are the typical presentation of Nicolau syndrome [10]. Nicolau syndrome, originally described in 1924 in syphilis patients who received an intramuscular injection of bismuth salts as treatment [11].

Other than intramuscular injection, intraarticular, subcutaneous and intravenous injections can also produce Nicolau syndrome [12]. Diclofenac induced Nicolau syndromes were reported by scientists [10-12]. The exact pathogenesis is still not completely elucidated; however, vasospasm secondary to needle prick, thrombophlebitis, pressure due to the material placed around the vessel (in case of intramuscular injection) are some factors contributing in the development of Nicolau syndrome[12, 13].

CONCLUSION: In the present study, drug-induced thrombosis and phlebitis are responsible for Nicolau syndrome. The actual composition of all three marketed diclofenac compounds was not known however propylene glycol is generally present in parental diclofenac injection [7] and their concentration plays a significant role in the development of thrombosis, phlebitis and other injection site reaction [7, 9]. Low concentration of propylene glycol in intravenous diclofenac injection produced a less adverse effect as compared to high propylene glycol concentration [7, 9]. In one study investigators [14] found that diazepam in propylene glycol developed a higher incidence of thrombophlebitis as compared to diazepam dissolved in oil and emulsified in water without loss of therapeutic effect. Among three marketed compounds, Voveran is recommended for intravenous infusion while Jonac AQ and Dynapar AQ are recommended for intravenous bolus and infusion. Hence, Voveran produced moderate to marked local injection site reaction in comparison to Jonac AQ and Dynapar AQ when administrated as an intravenous bolus. However, in a clinical trial, 51.4% of patients developed thrombophlebitis of various severities at the site of injection when Voveran administrated in recommended route [7]. In the present study, all three marketed injectable Diclofenac Sodium formulation (Jonac AQ, Dynapar AQ and Voveran) produced variable local injection site reaction as compared to normal saline group. Grossly and microscopically, among all three injectable Diclofenac Sodium formulations, the Voveran group produced more severe local injection site reactions followed by the Dynapar AQ group while Jonac AQ produced minimal to mild local injection site reaction.

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