Procedure-Related Findings Associated with Intravenous Injection in Non-Human Primates Utilized in Preclinical Toxicity Studies

Nick Vetter, Charlotte Hollinger, Keith Nelson
Inotiv, Kalamazoo, MI, USA

Figure 1: IV Injection Procedure-related Microscopic Findings

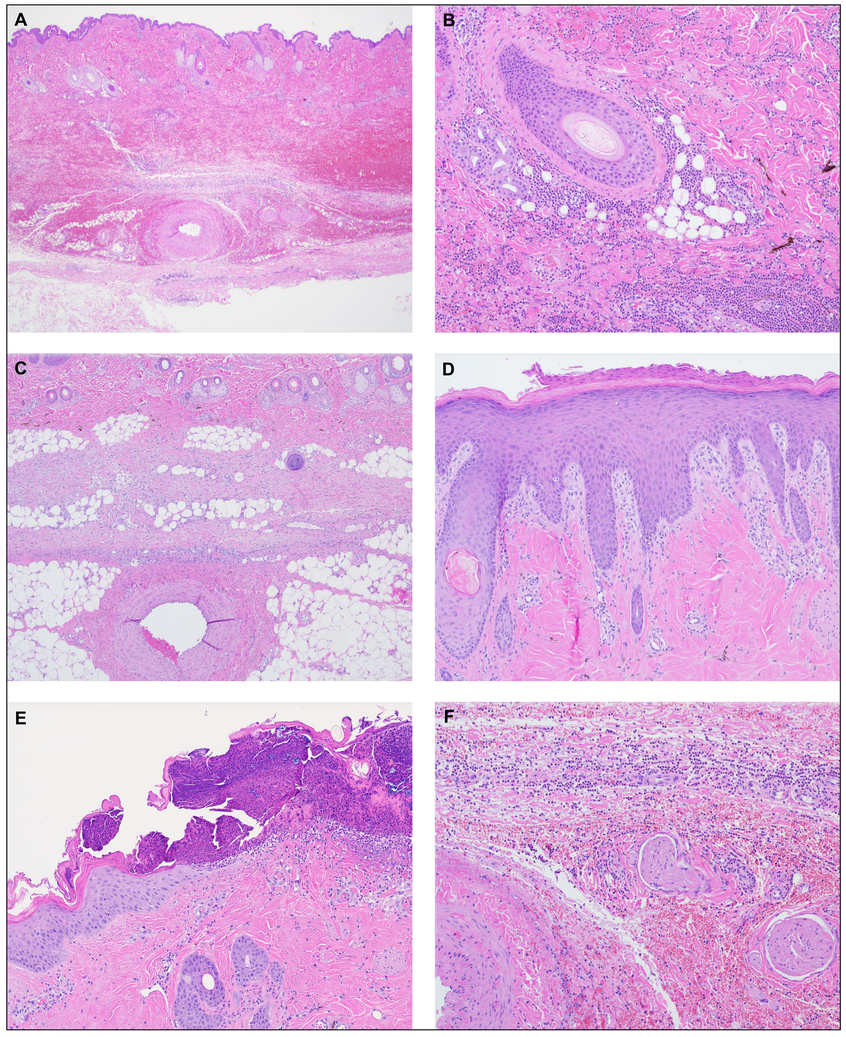

Figure 1: Procedure-related findings at the intravenous injection site commonly included hemorrhage (A and F); neutrophilic, mixed cell, or mononuclear infiltrate/inflammation (A-F); fibroplasia (C); and epidermal hyperplasia (D). Less common findings of edema (A), crust (E) and erosion/ulcer (E) were also reported.

Introduction

Recognition of test-article effects at the injection site and differentiation from procedure-related findings are imperative for accurate identification and reporting of potential toxicity in preclinical intravenous (IV) injection studies. Contemporary descriptions of procedure-related injection site findings in preclinical toxicity studies have predominately focused on subcutaneous or intramuscular injection or continuous rate infusion (CRI) utilizing an indwelling catheter system. Reports of findings related to non-CRI administration (i.e. IV bolus or temporary infusion catheterization) are limited in recent literature, particularly in non-human primates (NHPs). A retrospective review of historical control data was conducted to identify and describe acute procedural findings commonly observed with IV injections in NHPs.

Methods

Microscopic data from IV injection sites were compiled from 40 control Cynomolgus macaques (*Macaca fascicularis*) across seven (4 IV bolus, 3 IV infusion) good laboratory practice (GLP) toxicology studies finalized over two years (2023-2024). Study duration ranged from 3 to 183 days with single or repeat dosing, the latter ranging from weekly to every three weeks. Site of administration was the saphenous or cephalic vein and repeat dosing rotated between right and left sides. Only the most recent dose site was surveyed, and time since final dosing ranged from 1 to 7 days. Vehicle composition varied widely by study, including saline; histidine, trehalose dihydrate, and Polysorbate 20; arginine hydrochloride; Tris hydrochloride, 5% mannitol, and saline; and other test article-specific buffers. Duration of injection ranged from less than 1 minute IV bolus to 60 minutes short-term infusion via temporary (non-indwelling) catheter. Microscopic terminology for the included studies was reviewed and aligned based on In-Hand guidelines.

Results

Incidence and severity of findings were comparable between males and females. Common regional (cutaneous and/or subcutaneous) findings at intravenous injection sites (Table 1) included hemorrhage (42.5%), neutrophilic infiltrate (25.0%), and epidermal hyperplasia (22.5%); infrequent findings included mononuclear cell infiltrate (17.5%), mixed cell inflammation (17.5%), fibroplasia (12.5%), and mixed cell infiltrate (10.0%); and rare findings (<5%) included granulation tissue, crust, erosion/ulcer, edema, and necrosis. While a subset of findings were infrequently reported with perivascular distribution (infiltrate, mixed cell and granulation tissue), direct effects on the dosed blood vessel were not reported. Figure 1 comprises representative photomicrographs of select injection site findings, with all findings and their incidences summarized in Table 1.

Discussion

Acute IV injection site pathology in control NHPs reflects the initial inflammatory and tissue healing response to localized trauma from the injection procedure. Predominate microscopic findings include hemorrhage, leukocyte infiltration or inflammation, epidermal hyperplasia, and other changes associated with injury of the epidermis, dermis, and subcutis. Despite being relatively common in CRI studies, vascular findings localized to the administration site vein were notably absent among the reviewed studies. Injection site processing and examination guidelines between CRI and non-CRI studies are comparable, with targeted evaluation of the needle/catheter entry site and downstream/catheter tip region of the dosed blood vessel. The lack of distinct microscopic vascular findings among non-CRI studies suggests limited vessel injury associated with dosing compared to that from persistent catheterization. Otherwise, findings were similar to those reported in primates and non-primates under CRI study conditions. Consistent with other routes of administration utilized for injectable materials, there is significant overlap between these procedure-related microscopic findings and potential test article effects at the IV dosing site. As such, toxicologic pathologists evaluating IV injection studies should be familiar with typical microscopic findings associated with the non-CRI IV dosing procedure and remain vigilant for subtle differences between control/vehicle-dosed and test article-dosed animals to ensure accurate identification and characterization of toxicity at the injection site. Future efforts should focus on data set expansion, characterization and comparison of IV injection site findings in other species, and further comparison with other routes of injectable administration.

Table 1: IV Injection Procedure-related Microscopic Findings

	Sex	Males	Females
	Number Examined	20	20
Hemorrhage[a]			
	Minimal	2	3
	Mild	5	3
	Moderate	2	2
Infiltrate, Neutrophil[b]			
	Minimal	3	3
	Mild	1	1
	Moderate	1	1
Hyperplasia; Epidermis			
	Minimal	3	3
	Mild	1	1
	Moderate	0	1
Inflammation, Mixed Cell; Subcutis			
	Minimal	1	2
	Mild	3	1
Infiltrate, Mononuclear Cell[c]			
	Minimal	3	3
	Mild	0	1
Fibroplasia; Subcutis			
	Minimal	2	2
	Mild	0	1
Infiltrate, Mixed Cell[d]			
	Minimal	2	2
Granulation Tissue, Perivascular			
	Minimal	1	1
Crust			
	Minimal	1	0
Erosion/Ulcer; Epidermis			
	Minimal	1	0
Edema; Subcutis			
	Minimal	1	0
Necrosis; Subcutis			
	Minimal	0	0
	Mild	1	0

Findings ordered by incidence.
[a] Subcutis or not otherwise specified.
[b] Subcutis or dermis
[c] Subcutis, dermis, or not otherwise specified
[d] Subcutis or perivascular

References:

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