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MINIREVIEW

Current Perspectives on Pain upon Injection of Drugs

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Abstract ☐ A limitation in the administration of parenteral products is the pain caused upon injection. Injection site pain has been predominately associated with intravenous, intramuscular, and subcutaneous administration. It becomes important for the formulation scientist to have a basic understanding of the physiology underlying the pain process, as well as the pharmaceutical factors associated with injection site pain. Initially, this review will provide the reader with a primer on the mediation of pain in the periphery and a compilation of those drugs that have been associated with pain on injection. In addition, this review will present important considerations and general formulation approaches or methods that have been used to overcome pain on injection. Finally, a brief overview of the various experimental systems used to investigate injection site pain is discussed.

Introduction

Pharmaceutical formulators are increasingly being asked to investigate the use of parenteral routes of drug administration. One likely explanation is the increasing interest in the therapeutic development and use of peptide or protein drugs and gene delivery, which due to their limited oral bioavailability often require parenteral administration. Furthermore, the shift of patient care to the ambulatory setting has necessitated the investigation of the routes of drug administration that can be useful in the home health care environment for traditional small molecular weight molecules. Consequently, the formulator is often asked to provide successful short-term and/or long-term delivery of these therapeutic modalities, while maintaining stability and patient acceptability. The major routes of administration that have been utilized in preclinical and clinical trials are the intravenous, subcutaneous, and intramuscular routes of administration.[1] Other less commonly used routes include intraperitoneal, intrathecal, intracardiac, intracisternal, intralesional, intrapleural, intrauterine, and intradermal. However, these latter routes are frequently associated with specific drugs and therapies and limited to hospitalized patients.

From a formulator's perspective, the development of parenteral products requires optimization with respect to adequate stability, solubility, injectability, and tolerability of the therapeutic modality. The focus in the pharmaceutical literature, to date, has primarily been on understanding the factors and issues associated with developing formulations that achieve the requisite stability and solubility. It has also been critical to ensure the relative ease in the injectability of the product by minimizing viscosity or by providing guidelines on the safe route and rate of drug administration.

In contrast, pain or tissue damage upon injection of formulations (e.g., tolerability), while critical to the clinical (and even financial) success of these products, is less well understood by formulation scientists. The extent and

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mechanism of tissue irritation and/or damage following parenteral administration, as well as methods to minimize or eliminate these issues, have been discussed somewhat in the pharmaceutical literature.[2−8] However, the underlying factors responsible for pain upon injection, which may occur without direct toxicity to the injected tissue, have not received as much attention by formulators in the development of new products. Possible explanations for the limited knowledge in understanding the extent and mechanisms of injection-associated pain include (1) the lack in the number and type of models available to study the physiology and mechanisms of pain, (2) the difficulty, variability, and cost associated with using animal models to evaluate pain, and (3) the necessity to use subjective versus objective measures (which often involve extensive experimental setups) to evaluate the extent of pain and/or methods to reduce pain either in animals or humans.

While it is critical to characterize the extent of *pain* upon injection during the development of parenteral formulations, these studies are often not conducted due to the limitations described above. In contrast, the screening of formulations for their potential to cause *tissue damage* (e.g., hemolysis, muscle damage) can be done relatively easily using experimental systems which are readily available, require a short time frame, and include the appropriate positive and negative controls.[2−11] The question to be raised at this point is whether there is a relationship between pain and tissue damage. Three types of relationships between pain and tissue damage are possible and need to be considered. First, it is possible that a given formulation can cause tissue damage that results in pain at the injection site. If this were the case, screening of formulations for their potential to cause tissue damage provides a reasonable first approach to rule out unacceptable formulations. Use of tissue toxicity screening methods can provide the formulator with a rational approach to develop and select the optimal formulations with respect to the desired physicochemical properties and tissue tolerability.

Second, in contrast, there may be drugs or formulations associated with pain upon injection where there is no indication of any type of tissue damage at the site of injection. This relationship is more problematic because it is possible that formulations that did not cause tissue damage in preclinical studies are now reported to cause pain on injection during the subsequent clinical trials. If volunteers and patients report moderate or severe pain with injection during clinical studies, this could potentially stop or limit further development of the product. It would be useful in this case to have methods to screen a parenteral formulation early during development for the potential to cause pain.

Finally, it is possible for a given formulation to cause tissue damage that is not associated with pain upon injection. The difficulty in this particular scenario may occur if the formulation requires repeated injections that could cause irreversible changes in the tissue at the site. It subsequently becomes the responsibility of those individuals involved in the preclinical and clinical trials for drugs designed for repeated administration to include in their experimental methods the assessment of the long-term impact of repeated administration on tissue at the injection site.

Since at this stage the formulator cannot be sure of the relationship between tissue damage and injection site pain, it is recommended that studies investigating the extent of pain and or tissue damage be included during the design of parenteral formulations. Furthermore, it becomes critical for the formulator to be aware of the physiology associated with pain and the factors that have been reported to cause pain upon injection. The specific focus of this review will be to provide the formulator with (1) a basic primer to understanding the peripheral mediation of pain, (2) a discussion of those factors which have been reported to cause pain on injection, (3) a discussion of experimental systems to study pain on injection, (4) a report of those drugs reported to cause pain upon injection, and (5) a discussion on approaches which have been used to offset pain associated with injection. At this stage, there is no clear method that has been associated with a reduction of injection site pain.

For information on the specific methods to characterize the extent and mechanisms of *tissue damage* with parenteral administration, readers are referred to studies by Brazeau,[2,3] Gupta,[4] Comerski,[5] Sutton,[6−8] and Yalkowsky.[9−11]

The Mediation of Pain by the Peripheral Nervous System

The anatomy and physiology of the pain system will be limited to a discussion of the peripheral nervous system, as it is this component that has principal bearing on the pain upon injection. Where appropriate, suggestions of possible mechanisms by which a parenteral formulation could interact with the pain system will be briefly discussed.

The sensation of pain is mediated in the periphery by multiple sets of specialized afferents (sensory fibers) called nociceptors. Like other sensory neurons, nociceptor cell bodies are found clustered in paired ganglia located within each spinal vertebra (see Figure 1). Each ganglion cell has a peripheral process (axon) that extends out to tissue (e.g., muscle) and a central process that travels into the spinal cord to communicate with the central nervous system. Nociceptors have been subclassified on both anatomic and functional bases. The diameter of the peripheral process (1−15 μm) and the presence or absence of a nonneuronal covering (myelin) determine the rate at which afferents conduct impulses (action potentials). This forms the basis for anatomic criteria by which afferents are classified. It was formerly believed that pain sensation derived solely from the small diameter, slowly conducting, thinly myelinated and unmyelinated subgroups (called Aδ and C, respectively); however, recent evidence indicates that nociceptors are represented in all three major afferent categories. This includes the large diameter, fast conducting groups (Aβ), traditionally associated with touch sensation. It is worth noting that a parallel nomenclature is used for cutaneous (Aβ, Aδ, and C) and deep (muscle, viscera) afferents (group II, group III, and group IV). This distinction is mainly historical, as these classes are generally identical in function.[12−16]

While there is no absolute nomenclature for nociceptors, the most accepted naming system divides pain afferents according to their functional capacities. Therefore, nociceptors that respond to intense mechanical and thermal stimuli are mechanothermal nociceptors (MH). If they come from Aδ or C fiber groups, they are called AMH and CMH, respectively.[13] If they also have a chemical response, they are called polymodal nociceptors. Polymodal nociceptors are found in both myelinated and unmyelinated categories.[17,18]

Nociceptors are usually silent at rest. That is, in the absence of intense stimuli there is no activity. However, some nociceptors of the C (or group IV) class maintain a slow continuous activity rate (usually <1 Hz). It is important to note that even when stimulated, nociceptor activity is possible in all classes without any sensation. That is because activity in a nociceptive ending will not

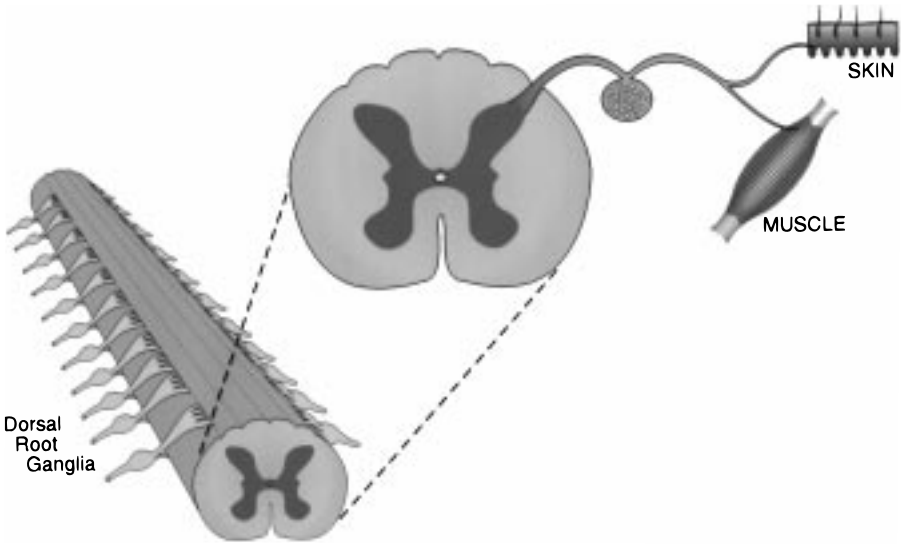

Figure 1—Innervation of tissue by peripheral afferents of the DRG. Pairs of dorsal root ganglia lie along the side of the spinal cord (left panel) and innervate peripheral tissues. Complimentary innervation of the head and oral tissues are supplied by paired trigeminal root ganglia. In the exploded section, innervation of muscle and skin are shown as relevant examples. Many thousands of cell bodies in each DRG contribute axons into peripheral nerves which have endings in all forms of peripheral tissue. Cell bodies for both nociceptive and non-nicoceptive sensoary afferents are found in the ganglia. Transduction (encoding) of sensory events occurs in the receptor ending (see Figure 2). The cell body synthesizes functional components of the neuron and ships them to both peripheral endings and to central synapses within the spinal cord.

necessarily be transmitted past the first relay in the spinal cord. Therefore, some critical level of activity is required before a sensation is reported. Once this critical frequency is achieved, the particular sensation is dependent upon the type of nociceptor activated. Different forms of sensation are associated with different subgroups. Activity in Aβ or Aδ nociceptors is associated with brief, intense burning (e.g., a match burn) or sharp, crushing or tearing sensations. Activity in C fiber nociceptors is associated with diffuse burning (e.g., sunburn) or aching sensations.[19,20]

Nociceptors are distinguished from other afferent groups (those mediating touch, tickle, pressure, warmth, cold) by their transducing (or encoding) capacity. All sensory afferents have characteristic response ranges that permit them to encode their preferred stimuli with precision. Accordingly, the range of neural discharge (action potential frequency in hertz) of nociceptors is tuned to reflect forces (or heat) that potentially damage tissue.[12,21,22] Therefore, nociceptors of the cornea are very sensitive and have a narrow response range while nociceptors of the skin have a very high threshold and broad response range.[21,23,24] Typically, nociceptor activity begins well before tissue damage is imminent but reaches a peak as tissue failure forces (tissue destruction) are approached.[22] This feature is important in understanding how injection volume can affect pain upon injection. The sensitivity of nociceptors to tissue distention is related to the fragility of the tissue injected. However, whether fragile tissues are stretched will be dependent upon the ability of the whole tissue to accept (disperse) large volumes of fluid without introducing tissue distortion into fragile tissue components. In this regard, it is important to remember that human tissue is generally a composite of both weak and tough components. This is one reason injection speed, injection volume, or site appears in some way to affect pain upon injection.

Nociceptor activation is ultimately dependent upon the ion channels present in the nociceptor endings (Figure 2). Mechanical nociception is dependent on the stretch-activated channels.[25,26] When mechanical forces in tissue grow (tissue is stretched or compressed), stretch-activated channels open and neural discharge is initiated. In addition to direct actions of fluid volume (see above), intense mechanical forces may be mimicked in nociceptor membranes when hyposmotic fluids force water into cells. Expansion of neural membranes, due to water entry, will have profound influences on nociceptor activity, because membrane stretch mimics intense mechanical forces in tissue. Similarly, hyperosmotic influences that draw water from neural endings could activate compression sensitive channels with similar consequences. However, compression sensitive channels are still hypothetical.

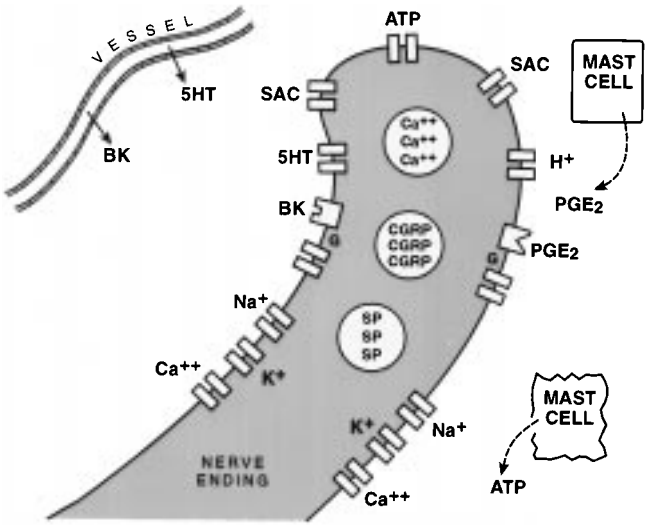

Figure 2—Simplified representation of the peripheral ending of a nociceptor. The drawing illustrates mechanisms by which nociceptor endings may interact with parenterals. These include interaction of the injected solution with the ending via pH or osmotic pressure, release of mediators from intact cells (e.g., PGE2), damaged cells (e.g., ATP), or from local vascular bed sources (5HT and BK). Weak passive currents evoked by these events may initiate action potentials at voltage activated Na^+ and K^+ channels. A minimum action potential frequency is required for perception. In the interest of simplicity, the nociceptor shown represents a composite of subtypes that include Aδ, C mechanothermal and chemically sensitive (polymodal) afferents. Specific receptors expressed for each ligand are shown by near association of the ligand. Some receptors form channels while other receptors are linked to channels by G proteins. Key: ATP, adenosine triphosphate; BK, bradykinin; Ca^{2+}, calcium; CGRP, calcium gene related peptide; G, G protein; H^+, proton; Na^+, sodium; K^+, potassium; PGE2, prostaglandin E2; SAC, stretch-activated channel; SP, substance P.

Thermal nociceptors are a major subgroup of the nociceptive population. The mechanism of thermal nociception is not known but may be due to the release of intracellular stores of Ca^{2+}.[27] Agents that release Ca^{2+} from intracellular stores (calcium ionophores) may mimic the thermal transduction response of nociceptors. The capacity of parenterals to release intracellular Ca^{2+} has not received attention but could explain the injection site pain associated with some agents.

As noted above, nociceptors that have chemical as well as mechanical and thermal response capacities are called polymodal. Mechanical and thermal responses are primarily designed to protect tissue from external, superficial stimuli. In contrast, chemical responses of nociceptors are designed to detect the aftermath of tissue damage. Vascular cells, inflammatory cells, and blood-borne precursors are sources of proinflammatory agents (e.g., bradykinin, serotonin, prostaglandins) that are recognized by nociceptors.[28] In addition, damaged cells release ATP, a potent activator of nociceptors. Specific receptors, present in nociceptor endings, recognize and bind these agents (e.g. bradykinin receptors, serotonin receptors, prostaglandin receptors, and ATP receptors).[29] Nociceptors are diverse in their expression of these chemical receptors. The binding of chemical agents results in ion flow that excites nociceptors, causes immediate pain, and can induce local and distal events that contribute to long term "soreness" or hyperesthesia. In addition, other receptors detect general tissue events associated with injury, such as decreased pH.[30] Tissue acidity increases when vascular supply is lost or diminished due to trauma. The introduction of parenterals, whose pH mimics a damaged environment, will open proton sensitive channels and powerfully activate nociceptors. If parenterals bring about tissue damage, proinflammatory agents will both directly activate nociceptors and contribute to hyperesthesia in the injection field. Central nervous system mechanisms are also likely to contribute to long-term soreness at injection sites.[31–32] Central nervous system (CNS) mechanisms of hyperesthesia are beyond the scope of this review. It is sufficient to recognize that these CNS mechanisms are dependent upon peripheral nociceptor activity for both initiation and maintenance.

Direct interaction of active drug, antimicrobials, or other additives with voltage activated ion channels is yet another means by which parenterals could influence the pain system. The nociceptive neuron is able to conduct signals (action potentials) because it has devised methods of separating ions (Na^+, K^+, Ca^{2+}) and controlling their flow across membranes through selective, voltage-activated ion channels.[33] In general, Na^+ flow favors signal generation and K^+ flow opposes signal generation. Nociceptors are activated, or their activity is modulated, by chemicals that interact with ion control mechanisms. The increase of ion flow in some channels (Na^+) or the decrease in ion flow in other channels (K^+) can cause or greatly enhance pain by modifying the range or rate of nociceptor discharge. Many naturally occurring and synthetic drugs interfere with ion control mechanisms at relatively low concentrations (micromolar to picomolar). The most well recognized of these are the plant and animal toxins. It is unclear to what extent drugs and/or formulation excipients in parenteral products could affect these ion control mechanisms.

Plants and animals have evolved chemical defenses or toxins [(e.g. capsaicin (plant toxin), melittin (bee toxin), dendrotoxin (snake toxin), charybdotoxin (a scorpion toxin)] that bind to ion channels or otherwise interact (or disrupt) nociceptor membranes.[34,35] By holding channels open (e.g., Na^+ channels) or preventing channels from opening (e.g., K^+ channels), plant and animal toxins are able to induce intense pain. Potentially, any foreign agent (e.g., antibiotic) introduced into tissue by injection could interact with ion channels by binding directly to the channel or blocking flow of ions through the channel pore. Agents could also interfere with the automatic "inactivation" process of ion channels (e.g., Na^+), thereby prolonging the duration of opening or preventing them from closing. Blocking of K^+ ion flow or increasing Na^+ ion flow could greatly enhance pain sensations either by directly activating nociceptors or increasing activity in those nociceptors which maintain a slow spontaneous discharge (see above).

Specific Mechanisms of Intramuscular and Subcutaneous Pain

Recent studies have investigated the specific mechanisms of intramuscular and subcutaneous pain. Graven-Nielson and co-workers have examined the factors associated with muscle pain in humans using hypotonic, isotonic, and hypertonic saline solutions by using microdialysis.[36–37] It was reported that only a hypertonic saline solution resulted in increased intramuscular pressure and that pain activation in skeletal muscle is related to increased sodium and potassium content.[36] Furthermore, it appears that intramuscular pain is increased by temporal (repeated injections) and spatial summation (injections given at different sites).[37] For subcutaneous injections, pain appears to be reduced when a buffer at a nonphysiological pH is prepared at a lower buffer capacity, to enable a more rapid normalization to the pH at the injection site.[38] Jorgensen and co-workers have reported that pain following subcutaneous administration is related to the injection volume.[39]

Compounds Reported to Cause Pain on Injection

A wide variety of drug classes have been reported to cause pain following parenteral administration. This list includes antibiotics, benzodiazepines, vitamins, iron, nonsteroidal antiinflammatory agents, phenothiazines, local and general anesthetics, anticonvulsants, and peptide drugs. The drugs or formulations reported to cause pain, and potential strategies to reduce this event, are listed in Table 1.[40–128] A review of this list indicates that pharmacological agents associated with pain on injection include a broad array of those used in clinical practice. Furthermore, the diversity in the structures does not seem to indicate specific chemical moieties or properties that can be linked to injection-associated pain. The reports of pain on injection seem to be the greatest with the penicillin, cephalosporin, and aminoglycoside antibiotics. In addition, the general anesthetics also seem to be associated with pain upon iv injection. It is unclear whether this would be primarily a function of their specific chemical structure, properties, and/or their formulations or secondary to the widespread use of these agents in hospitalized and ambulatory patients.

The formulator must be keenly aware of the difficulty in interpreting some of these experimental findings. It is critical for the formulator to discriminate the painful effect of the drug from that of the other excipients in the formulation. There is usually no problem when the drug is hydrophilic and can be readily formulated to achieve the desired pharmaceutical properties using an isotonic vehicle that is not associated with pain (e.g., normal saline). In contrast, for more lipophilic compounds that may require solubilization, complexation, or emulsification, it may be extremely difficult to determine the magnitude of pain associated with the injection of the drug molecule itself. It

Table 1—Drugs Reported To Cause Pain upon Injection[a]

drug class and specific agents	nature of pain response	method of reducing adverse response	ref no.
	Penicillin Antibiotics		
amoxicillin	1/3 patients pain upon injection	include lidocaine or procaine HCl	40
penicillin G	irritating after im injection, sciatic nerve damage, irritation and dysfunction possible	include procaine	41
penicillin G benzathine	pain after sc and im injection	none suggested	41
penicillin G procaine	pain after im injection	none suggested	41
sodium sulbactam and ampicillin	pain at im site	none suggested	42
	Cephalosporin Antibiotics		
cefamandole	pain at im site	inject deeply into large muscle mass	43
cefoperazone	transient pain at im site	include lidocaine	43
cefotetan disodium	pain at injection site	include lidocaine	43
cefoxitin	pain at im site	none suggested	44
ceftazidime sodium	pain at im site	none suggested	43
ceftriaxone	pain upon injection	include lidocaine	45
ceftriaxone	pain at im site	none suggested	46
ceftriaxone	pain at im site	use lidocaine or buffered lidocaine	47
cefuroxime sodium	pain at im site	less painful when injected as a suspension rather than a solution, less pain when injected into the gluteus maximus or the vastus lateralis	43
	Aminoglycoside Antibiotics		
amikacin sulfate	local irritation and pain after im and iv administration	none suggested	48
gentamicin sulfate	local irritation and pain after im and iv administration	none suggested	48
kanamycin sulfate	local irritation and pain after im and iv administration	none suggested	48
neomycin sulfate	local irritation and pain after im and iv administration	none suggested	48
streptomycin sulfate	local irritation and pain after im and iv administration	none suggested	48
timoxicillin	pain on im injection	none suggested	49
tobramycin sulfate	local irritation and pain after im and iv administration	none suggested	48
	Antimalarials		
arthemether	pain at im site	none suggested	50
	Aminocyclitrol Antibiotic		
spectinomycin	pain at im injection site	none suggested	51
trospectomycin	pain and tenderness at im injection site	none suggested	52
	Tetracycline Antibiotics		
tetracycline	pain at im site	inject deeply into large muscle	53
	Antiprotozoals and Antihelmintic		
pentamidine	pain on im injection site	iv infusion	54
oxamniquine	moderate to severe pain at im site for days to weeks	none suggested	55
	Macrolide Antibiotics		
clarithromycin	pain on iv injection	formulate as an emulsion	56
	Antineoplastics		
bleomycin	pain on intralesional injection	include lidocaine	57
methotrexate	pain at im site	subcutaneous injection	58
	Benzodiazepines		
diazepam	pain on injection	formulate as an emulsion	59
diazepam	pain on injection	formulate as an emulsion	60
diazepam	pain and thrombophlebitis on injection	formulate as an emulsion	61
diazepam	pain and thrombophlebitis on injection	formulate as an emulsion	62
diazepam	pain on injection	formulate as mixed micelles	63
lorazepam	pain at im site	use sublingual administration	64
midazolam	pain during im injection	none suggested	65
	Phenothiazines		
chlorpromazine	irritation after sc injection, pain after im injection	include procaine	66
promethazine HCl	irritation following sc injection	none suggested	67
	Local Anesthetics		
bupivicaine	pain on sc injection	adjust pH to 7.0	68
lidocaine	pain on iv injection	increase pH	69
lidocaine	pain on sc injection	addition of sodium bicarbonate	70
lidocaine	pain on sc injection	warm solution	71
	General Anesthetics		
etomidate	pain on iv injection	none suggested	72
etomidate	pain on iv injection	none suggested	73
etomidate	pain on injection	none suggested	74
methoxital	pain on injection	formulate as an emulsion	75
methohexitone	pain on iv injection	include lidocaine	76
propofol	pain on injection	include alfentanil	77
propofol	pain on iv injection	include lidocaine	78
propofol	pain on iv injection	include lidocaine or procaine	79
propofol	pain on iv injection	use antecubital fossa as injection site	80

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