莫西菌素药效学与药动学研究进展

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摘要 莫西菌素是一种半合成的单一成分的大环内酯类抗寄生虫药,其药代动力学特征与药效密切相关。通常莫西菌素药代动力学会因制剂、动物品种、机体状态以及与其他药物的相互作用而发生改变。综述了莫西菌素药效学和药代动力学,为莫西菌素的临床应用提供参考。

关键词 莫西菌素;药效学;药动学;抗寄生虫药
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Advances in Pharmacodynamics and Pharmacokinetics of Moxidectin

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Abstract Moxidectin is a semi-synthetic mono-component macrolide antiparasitic drug. The pharmacokinetic characteristics of moxidectin are closely related to its efficacy. In general, the pharmacokinetics of moxidectin are changed by the formulations, breeds, body status and interaction with other drugs. This article reviewed the pharmacodynamics and pharmacokinetic of moxidectin. It was refered to the clinical application of moxidectin.

Key words Moxidectin; Pharmacodynamics; Pharmacokinetics; Antiparasitic drug

莫西菌素(moxidectin,MXD),又称为莫昔克丁或莫西克汀,是由链霉素发酵产生的半合成单一成分的大环内酯类抗生素。MXD 属于米尔贝霉素(milbemyeins)家族,是奈马菌素(nemadectin)的衍生物,属于第三代阿维菌素类(AVMs)药物。MXD 与其他 AVMs 相比,MXD 成分单一,具有驱虫谱广,驱虫活性强、长效、安全[1]等特点。与伊维菌素(ivermectin,IVM)相比,MXD 能与多种赋型剂组合制成各类制剂,可供开发选择剂型的范围更广。目前,临床上常用的 MXD 剂型有浇泼剂、注射剂、片剂、透皮剂、口服凝胶等,其被用于牛、羊、马、猪、犬、猫等动物寄生虫病的防治,甚至用于人的盘尾丝虫病的治疗[2-3]。MXD 是理想的体内外抗寄生虫药物。该研究拟综述莫西菌素药效学和药代动力学,以期为莫西菌素的临床应用提供参考。

1 MXD 理化性质

MXD 分子式为 $C_{37}H_{53}NO_8$,分子量为 639.8 g/mol。它的结构类似于 IVM 的 B1,不同处是在 C_{13} 上没有双糖,在 C_{25} 上有一个含烯烃的链,在 C_{23} 上有一个甲氧基(图 1)。MXD 元素组成 C 为 69.48%、H 为 8.37%、N 为 2.15%、O 为 20%(试验数据)。其性状为白色或淡黄色无定型粉末,熔点为 145~154 ℃,酸离解常数(pKa)为 12.8±1.0,蒸汽压< 10^{-7}(检测极限)。差示扫描量热法(DSC)测定 MXD 的最大电热融化温度为 274.6 ℃,能量为 492.1 J/g。MXD 不溶于水,微溶于正己烷,易溶于乙醇(> 96%)、乙腈、乙酸乙酯等有机溶剂。MXD 的正辛醇/水分配系数(58 300)显示为亲脂性化合物,其亲脂性为 IVM 的 100 倍以上。MXD 紫外可见吸收波长在 243.8 nm 出现最大吸收峰。MXD 在酸、碱、光照及氧气存在的条件下均不稳定,在制备过程中需要考虑这些因素对制剂稳定性的影响[4]。MXD 在水中溶解度低,无挥发性,不会通过空气迁移,故排出到环境中的 MXD 与土壤结合较紧密。莫西菌素在环境中发生代谢、吸收以及光降解作用,对环境造成污染的可能性非常小。

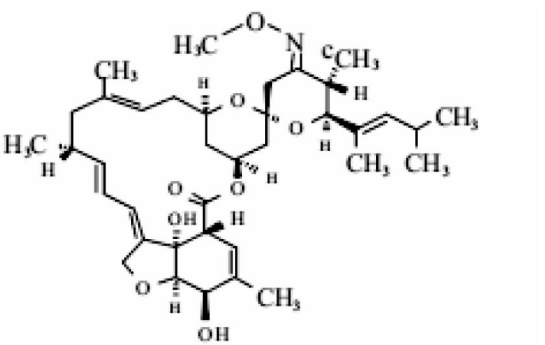

图 1 莫西菌素分子式

Fig. 1 Molecular formula of moxidectin

2 MXD 药效学

2.1 MXD 抗虫谱 MXD 对多种动物的体内消化道线虫与体表寄生虫均有较强的驱虫作用。对牛羊体内的捻转血矛线虫、古柏线虫、毛圆线虫、仰口线虫、细颈线虫、食道口线虫、网尾线虫等[5-6];对猪体内的蛔虫、毛首线虫、食道口线

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虫、后圆线虫等;对犬的心丝虫、结膜吸吮线虫、血管圆线虫、毛细线虫等[7];对多种动物体表的蠕形螨、疥螨、虱、蚤、蝇蛆等节肢动物均具有很强的杀灭作用[8]。

2.2 MXD 驱虫作用 Fazzio 等[9]用 MXD 治疗自然发病感染捻转血矛线虫(*Haemonchus* spp.)和古柏线虫(*Cooperia* spp.)的育肥犊牛,平均粪便卵计数(FECs)降低 85%。Rizk 等[10]发现 MXD 对水牛犊牛感染弓形虫的驱虫活性强且持久。用 1%的 MXD 注射液(CYDECTIN-Ford Dodge)治疗患有严重疥螨疾病的山羊,首次给药后皮肤瘙痒症已迅速减轻,治疗 8 周后,所有羊均治愈[11]。Demeulenaere 等[12]报道了 MXD 对寄生于马的大多数寄生虫表现出比 IVM 更长的保护时间。

MXD 不仅应用于大动物的寄生虫病防治,而且在防治小动物寄生虫病方面也应用广泛。用含 MXD 成分的爱沃克[Advocate® ,10%吡虫啉(Imidacloprid)+2.5%MXD]治疗由毛细线虫引起的犬鼻毛细血管病,在给药第(28±2)天的粪便中卵囊数减少了 99.14%[13]。用 MXD 缓释制剂和口服制剂预防临床分离耐 IVM 的心丝虫人工感染犬,防治效果分别达 99.5%和 100%[14-15]。爱沃克在连续给药 8 周后,治疗肾上腺皮质功能亢进继发性全身蠕虫病(蠕形螨)的犬的治愈率为 90.1%,并有效维持 1 年的时间[16]。AdvantageMulti® for Cats(10% Imidacloprid+1% MXD)对猫自然感染嗜气毛细线虫(*Capillaria aerophila*)的治疗效果达 100%[17],对猫耳螨(*Otodectes cynotis*)的治疗效果为 100%,并且持续到第 50 天[18]。

MXD 的驱虫作用与其本身具有良好的抗寄生虫活性,临床的合理使用能提高其驱虫效果。MXD 的药代动力学受到禁食、动物脂肪沉积厚度等生理状态以及 P-gp 调节剂的影响(在药代动力学部分具体阐述),使用时依据动物生理状态以及药物的配伍提高其临床疗效。另外,可以结合地域与动物的养殖特点,在特定的周期内使用,提高 MXD 的抗寄生虫效果。如对高海拔区域放牧的羊群,母羊围产期暂时对肠道线虫感染的抵抗力下降,导致粪便中卵囊数增加[19]。母羊排出的虫卵不仅污染牧草,而且孵出的感染性幼虫感染羔羊[20-21],给羊群寄生虫病防治带来一定困难。围产期使用 MXD 可以有效防治羊群的寄生虫疾病,也可以减少虫卵对牧场的污染[22]。在临床应用中,MXD 的给药方案以及适当时期使用对于寄生虫控制有着非常重要的意义。

3 MXD 药代动力学

3.1 MXD 药代动力学特征

3.1.1 吸收。达峰时间(T_{max})可以反映药物在体内吸收的快慢。MXD 在体内的吸收比其他 AVMs 药物快。Lanusse 等[23]报道了 MXD、IVM 和多拉菌素(doramectin,DRM)在牛体内的 T_{max} 差异,MXD 的 T_{max}(8.0 h)要早于 IVM(4 d)和 DRM(6 d)的 T_{max}。MXD 皮下给药后在不同动物体内 T_{max} 先后顺序为安格斯牛>荷斯坦牛>羊驼>骆驼>绵羊>袋熊>马鹿>杂交小牛>山羊(表 1)。从表中可以看出 MXD 在山羊体内 T_{max} 最快。

3.1.2 分布和代谢。MXD 在体内分布广泛,在脂肪、黏膜、胆汁、血浆、毛皮等组织中均有分布[31]。由于 MXD 具有高脂溶性和对脂肪组织高亲和力,MXD 主要分布在脂肪组织[32]。MXD 给药后,在脂肪组织中的浓度最高,依次为肝脏、肾脏和肌肉[33]。

表 1 MXD 吸收相关的药代动力学参数

Table 1 Pharmacokinetic parameters related to absorption of MXD

动物 Animal	达峰浓度 C_{max} ng/mL	达峰时间 T_{max} d	药时曲线下面积 AUC ng·d/mL	参考文献 Reference
马鹿 Red deer	71.80	0.50	106.60	[24]
绵羊 Sheep	8.29	0.88	112.33	[25]
山羊 Goat	24.30	0.36	136.70	[26]
安格斯牛 Angus cattle	2.33	5.00	21.68	[27]
荷斯坦牛 Holstein cattle	5.08	2.06	41.20	
杂交小牛 Crossbred calves	43.20	0.40	164.00	[5]
羊驼 Alpaca	4.40	1.75	61.87	[28]
骆驼 Camel	8.73	1.00	70.62	[29]
袋熊 Wombat	98.60	0.57	377.60	[30]

MXD 代谢的主要器官为肝脏,肝脏中细胞色素 P450 主要参与 MXD 的代谢[34]。MXD 的代谢物包含 1 种羟基化代谢物和至少 6 种其他的代谢物[35]。MXD 在牛体内的主要代谢产物为 C_{29-30} 和 C_{14}-羟甲基衍生物[36]。由于动物品种的差异,MXD 在肝脏中生物转化的快慢存在一定差异,从而影响 MXD 在体内的滞留时间。Dupuy 等[37]报道使用几种动物的肝微粒体,在体外研究对^{14}C 标记的 MXD 的生物转化率,结果显示,绵羊的生物转化率最高(32.7%),而猪的生物转化率最低(0.8%),其他动物的生物转化率依次为牛(20.6%)、鹿(15.4%)、山羊(12.7%)、兔子(7.0%)和大鼠(3.0%)。

3.1.3 排泄。MXD 主要是通过粪便排出体外(>95%),仅有少量通过尿液排泄(<1%)。通过检测公牛粪便,在第 7、14、28 天排出 MXD 的量分别相当于给药剂量的 32.2%、41.3%和 58.1%[35]。但是在哺乳期时,MXD 也能通过乳汁排出[38],吮吸乳汁的幼畜体内能检测到 MXD[39]。骆驼乳汁中的 MXD 药代动力学参数 C_{max} 和 AUC 是血浆中 C_{max} 和 AUC 的 3~4 倍[40]。MXD 通过乳汁排泄,与 MXD 的高脂溶性特征有关。

3.2 影响 MXD 药代动力学参数的因素 MXD 的药代动力学因机体状态、给药途径、药物剂型的不同而有明显差异,给药前是否禁食和额外补充油脂以及药物的相互作用也能对动力学参数产生明显影响。

3.2.1 机体状态。动物不同年龄、性别、生理、病理因素等均会影响 MXD 的药代动力学特征(表 2)。Craven 等[41]研究表明肥猪(背膘厚)MXD 的 C_{max} 比瘦猪低,但全身循环的药物总量显著升高;肥猪 MXD 的体清除率(CL/F)低,平均滞留时间(MRT)长,说明 MXD 在肥猪体内更长效。雌性比格犬的 MXD 吸收较雄性比格犬慢,C_{max} 低,分布较广,全身循

环的药物总量多,清除缓慢[42]。羔羊的 MXD 吸收更快,C_{max} 更高,但到达全身循环的药物总量显著降低[43]。怀孕动物体内 MXD 的消除速度加快,缩短 MXD 在体内的 MRT[44]。感染寄生虫的羔羊组皮下注射 MXD 的 AUC 比健康组降低了 2 倍,MRT 显著缩短。羊患寄生虫病后引起了 MXD 的 CL/F 增加,伴随着消除半衰期($T_{1/2\beta}$)缩短,导致体内 MRT 缩短,缩短了药物正常的维持时间[45]。

MXD 的药代动力学参数除受到上述因素影响外,还受到给药前是否禁食以及额外补充油脂的影响。禁食减少胆汁分泌和肠蠕动[46],增加了 MXD 在肠道停留时间,延长了 MXD 的吸收,提高了 MXD 的 AUC。额外饲喂油脂,给药后 MXD 的 AUC 会增加。Bassissi 等[47] 研究了试验前饲喂 10 g 葵花籽油的新西兰兔体内 MXD 的药代动力学,对照组 MXD 的 AUC[8.62 (ng·d)/mL]低于饲喂葵花籽油饲组[17.07 (ng·d)/mL]。因此,给药前额外补充饲喂油脂可以改善 MXD 的口服生物利用度,这与 Cotreau 等[48] 的报道相一致。MXD 的生物利用度增加可能与 MXD 在小肠中的吸收增加有关[49-50]。

表 2　机体状态对 MXD 药代动力学参数的影响

Table 2　Effect of body status on pharmacokinetic parameters of MXD

动物 Animal	给药途径 Route	剂量 Dose mg/kg	达峰浓度 C_{max} ng/mL	达峰时间 T_{max} d	药时曲线下面积 AUC ng·d/mL	消除半衰期 $T_{1/2\beta}$ d	平均滞留时间 MRT d	参考文献 Reference
羔羊 Lamb	PO	0.20	13.02	0.65	52.58	18.03	7.96	[45]
	PO[A]	0.20	9.28↓	0.61	28.76↓	7.73↓	2.93↓	
	SC	0.20	36.31	0.04	253.36	0.98	10.84	
	SC[A]	0.20	55.49↑	0.08↑	119.06↓	1.77↑	3.66↓	
绵羊 Sheep	SC	0.20	8.40	0.49	109.80	17.89	27.40	[44]
	SC[B]	0.20	8.00	0.40	143.60↑	11.49↓	20.60↓	
羔羊 Lamb	SC	0.20	7.40	0.80	78.50	9.00	—	[51]
绵羊 Sheep	SC	0.20	8.40	0.49↓	109.80↑	17.89↑	27.40	[44]
比格犬	PO[C]	0.25	263.00	0.09	529.17	12.74	—	[42]
Beagle dog	PO[D]	0.25	243.00	0.11	570.83	21.37↑	—	
猪 Pig	SC[E]	0.30	91.30	0.033	113.00	—	5.25	[41]
	SC[F]	0.30	72.10↓	0.031	222.08↑	—	7.92↑	
	SC[G]	0.30	26.00	0.24	274.00	—	22.30	[52]
	SC[H]	0.30	29.10↑	0.24	436.00↑	—	18.70	
兔 Rabbit	PO[I]	0.30	7.63	0.66	17.07	5.89	2.12	[47]
	PO[J]	0.30	7.44	0.31	8.62	3.85	1.52	
人 Human	PO[K]	0.80	79.10	0.22	203.54	29.16	—	[49]
	PO[L]	0.80	58.90	0.15	141.13	32.67	—	

注:A 表示线虫感染的羔羊;B 表示怀孕的绵羊;C 为雄性;D 为雌性;E 为瘦猪;F 为肥猪;G 表示饲喂低纤维/高脂肪的日粮;H 表示饲喂高纤维/低脂肪的日粮;I 表示 MXD 给药前 15 min 饲喂了 10 g 的葵花籽油;J 表示 MXD 给药前饲喂 10 mL 的水;K 表示高脂肪早餐;L 表示禁食。“—”表示未知数据

Note:A. Nematodes infected;B. Pregnant sheep;C. Male;D. Female. E. Thin-backfat thickness;F. Fat-backfat thickness;G. Fed a low fiber/high fat grower ration;H. Fed a low fat/high fiber maintenance ration;I. Sunflower oil(10 g) was administered at 15 min before MXD administration;J. Water(10 mL) was received at 15 min before MXD administration;K. High-fat breakfast feeded;L. Fasted;“—” was unknown data

3.2.2　给药途径。给药方式不同会造成 MXD 在体内的药代动力学差异。对牛单次皮下注射 MXD 时,在给药后的 4~6 h 达到 C_{max};单次口服给药后 C_{max} 出现在给药后 24 h。与口服组相比,MXD 皮下给药的半衰期更长,体内药物循环总量更大,MRT 更长,相对生物利用度更高[51]。MXD 液体制剂口服后的 C_{max} 和 AUC 分别比片剂的高 28.6%和 28.8%,T_{max} 缩短了 0.9 h[50],这可能与液体制剂提高 MXD 的溶解度有关。

3.2.3　剂型。除了给药途径对 MXD 药代动力学影响外,MXD 的制剂类型也对其药代动力学产生较大的影响。Dupuy 等[53] 报道了莫西菌素长效制剂(LA)在牛中的药代动力学(1 mg/kg 的 LA 莫西菌素生物利用度相当于皮下给予 0.2 mg/kg 常规莫西菌素制剂的生物利用度),LA 莫西菌素的 C_{max} 增加了 40%,T_{max} 延迟了 1 062%,MRT 增加了 198%,AUC 增加了 450%以上[23]。由于 MXD 具有较高的脂溶性,适合开发长效制剂,提高其驱虫作用和生物利用度。

3.2.4　药物相互作用。P-糖蛋白(P-glycoprotein,P-gp)是跨膜蛋白,能够将多种结构化合物泵出细胞外[54]。目前,已有 MXD 与不同的 P-gp 调节剂在动物体内相互作用的研究报道[55]。牛皮下注射 MXD 并联合使用洛哌丁胺(loperamide,LPM),联合用药组牛血浆中 MXD 的浓度明显高于单独 MXD 皮下注射组。MXD 和 LPM 合用还导致 AUC 升高和 CL/F 降低[56]。LPM 提高了 MXD 在牛体内的生物利用度。与 LPM 不同的是,MXD 和酮康唑联合给药,MXD 的血浆浓度与羔羊中单独使用 MXD 的浓度没有差异[57]。因维拉帕米的半衰期短,发挥的作用时间较短暂,故维拉帕米对绵羊 MXD 药代动力学没有产生明显的影响[58]。体外研究表明,MXD 与 AVMs 化合物相比,对哺乳动物 P-gp 亲和力较低[59],这可能是 MXD 在动物体内维持较长时间的原因之一[60]。

4　展望

由于 IVM 和阿维菌素(avermectin,AVM)广泛使用,已有

寄生虫对 IVM 和 AVM 产生耐药性的报道[60-62]。尽管 MXD 对 P-gp 的亲和力较低,相对于 IVM 不容易产生耐药性[55],但是 MXD 与 IVM 和 AVM 有交叉耐药性,近几年也出现了 MXD 耐药性的报道[63]。MXD 缓释制剂是提高防治动物寄生虫病、减少耐药性产生的策略之一。常规制剂由于维持作用的时间较短,需要频繁给药,且体内的血药浓度变化较大。这种频繁给药频率与耐药性线虫的出现之间存在一定的关系[64]。缓释制剂维持的有效时间覆盖在动物整个胃肠道线虫发育的各个阶段,可以减少耐药性的产生。目前,关于缓释制剂的开发有大量的文献报道,如长效注射液、注射用凝胶制剂、微球凝胶(MS-Gel)制剂[65]等。纳米化技术是提高水不溶性 MXD 生物利用度的一种有前景的制备策略,因为它可以提高 MXD 的溶解度和吸收。脂质体纳米颗粒载体也可用于透皮制剂,以改善药物的生物利用度[66-68]。MXD 的疗效与寄生虫是否产生耐药性直接相关,大多数认为 MXD 剂量不足可能是导致耐药性的重要因素。如何提高 MXD 的疗效并延缓耐药性的发展是新制剂设计中要考虑的重要因素。

MXD 作为新一代驱虫抗生素,能高效杀灭体内外寄生虫。MXD 在用药剂量、剂型开发、耐药性和体内药物分布等方面优于 IVM,是一种应用前景广阔的抗寄生虫药。尽管 MXD 具有很好的驱虫活性及驱虫谱,但也难免存在耐药性。长效缓释制剂的开发、临床合理用药是减少 MXD 耐药性的有效手段。MXD 的药代动力学受多种因素的影响,例如品种、身体状况、给药途径等,临床应充分考虑这些因素,以提高 MXD 的临床治疗效果。

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