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二甲基亚砜毒性研究*

王 洁 郝彩丽 孙红军 张心怡 李红娟

(西安市儿童医院耳鼻喉头颈外科 陕西 西安 710003)

摘要:二甲基亚砜(Dimethyl sulfoxide DMSO)是一种含硫有机化合物,被誉为“万能溶剂”,广泛用作溶剂和反应试剂。在医药工业中,DMSO可直接用作某些药物的原料及载体。DMSO本身有消炎止痛,利尿,镇静等作用,亦誉为“万灵药”,常作为止痛药物的活性组分添加于药物之中。DMSO也是一种渗透性保护剂,能够降低细胞冰点,减少冰晶的形成,减轻自由基对细胞损害,改变生物膜对电解质、药物、毒物和代谢产物的通透性。DMSO作为组蛋白去乙酰化酶抑制剂(Histone Deacetylases-inhibitor HDACi)的一种,同样具有恢复组蛋白的乙酰化与去乙酰化平衡,抑制细胞程序性死亡,修复DNA双螺旋结构,抗放射性损伤,抗炎反应及抗癌作用。鉴于其应用广泛,本文就其物理特性及毒性研究做一综述。

关键词:二甲基亚砜;毒性;物理特性

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Dimethyl Sulfoxide Toxicity Studies*

WANG Jie, HAO Cai-li, SUN Hong-jun, ZHANG Xin-yi, LI Hong-juan

(Otolaryngology-Head & Neck Surgery, xi'an children's hospital, Xi'an, Shaanxi, 710003, China)

ABSTRACT: Dimethyl sulfoxide (DMSO) is a sulfur-containing organic compounds, known as "universal solvent", it is widely used as solvents and reagents. In the pharmaceutical industry, DMSO can be directly used as a raw material and a carrier of certain drugs. DMSO has anti-inflammatory analgesic, diuretic, sedative and other effects, also known as "panacea", often used as an active component of analgesics being added to the drug. DMSO is a permeable protective agent, can reduce cell freezing point, reducing the formation of ice crystals, reduce free radical damage to cells, and change the permeability of membrane of electrolyte, drugs, poisons and metabolites. DMSO as one of the histone deacetylase inhibitor (Histone Deacetylases-inhibitor HDACi), also can restore histone acetylation and deacetylation balance, inhibit programmed cell death, repair DNA double helix structure, anti-radiation injury, anti-inflammatory and anti-cancer effects. Because of its widely applications, we do a review on its physical characteristic and toxicity studies.

Key words: DMSO; Toxicity; Physical characteristic

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二甲基亚砜(Dimethyl sulfoxide DMSO)是一种含硫有机化合物,分子式为 C_2H_6OS ,结构简式: $(CH_3)_2S-O$,常温下为无色无臭的透明液体,是一种吸湿性的可燃液体。具有高极性、高沸点、热稳定性好、非质子、与水混溶的特性,能溶于乙醇、丙醇、苯和氯仿等大多数有机物,被誉为“万能溶剂”。二甲基亚砜广泛用作溶剂和反应试剂,特别是丙烯腈聚合反应中作加工溶剂和抽丝溶剂,作聚氨酯合成及抽丝溶剂,作聚酰胺,聚酰亚胺和聚砜树脂的合成溶剂,以及芳烃,丁二烯抽提溶剂和合成氯氟苯胺的溶剂等。除此之外,在医药工业中二甲基亚砜还有直接用作某些药物的原料及载体。二甲基亚砜本身有消炎止痛,利尿,镇静等作用,亦誉为“万灵药”,常作为止痛药物的活性组分添加于药物之中。二甲基亚砜也是一种渗透性保护剂,能够降低细胞冰点,减少冰晶的形成,减轻自由基对细胞损害,改变生物膜对电解质、药物、毒物和代谢产物的通透性。二甲基亚砜作为组蛋白去乙酰化酶抑制剂(Histone Deacetylases-inhibitor HDACi)^[1]的一种,同样具有恢复组蛋白的乙酰化与去乙酰化平

衡,抑制和对抗可能由氧化损伤机制导致的肺癌^[2],导致肿瘤细胞HL-60的程序性死亡^[3],修复DNA双螺旋结构,抗放射性损伤^[4]抗炎反应^[5]抗癌^[6,7]于其应用广泛,本文就其物理特性及毒性研究做一综述。

1 DMSO 的物理特性

关于DMSO的一些物理特性,总结于下面的表格中(见表1)。

2 急性毒性

通过单次给药的半数致死量(LD-50, Lethal Dose-50)来评估危险性。半数致死量指在标准条件下一次给药DMSO(g/kg)必然引起50%的测试动物死亡的剂量。不同实验室提供的数据也许不完全相同,但是,都证实了DMSO的低毒性。DMSO作为非水溶性碘化试剂的溶剂静脉内给药证实其安全性^[8]。将部分数据总结于表2:不同种属,不同给药方式下,一次给药的半数致死量(Table 2 Different species and different mode of treatment,

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作者简介:王洁(1981-),女,硕士,主治医师,主要从事过敏性鼻炎的基础与临床研究,电话:029-87692055, E-mail:89042345@qq.com

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the Single-Dose Toxicity of DMSO as LD-50)。

表 1 二甲基亚砜的物理特性

Table 1 Physical Properties of DMSO

Physical Property	Metric Units
Freezing Point	18.55℃
Boiling Point - 760 mm	189℃
Vapor Pressure - 0.6 in Hg	25℃
- 13 Hg	100℃
- 310 Hg	150℃
optical density(g/mL,20/4℃)	1:100
Auto-ignition Temperature in Air	300-302℃
Flash Point (open cup)	95℃
lash Point (closed cup)	89℃
Flammability Limits in Air -	
Lower (100℃)	3-3.5% by volume
Upper	42-63%
Heat of combustion	
(KJ/mol, metered volume)	1793.16

表 2 不同种属的,不同给药方式下,一次给药的半数致死量

Table 2 Different species and different mode of treatment, the Single-Dose Toxicity of DMSO as LD-50

Species	Single-Dose Toxicity of DMSO as LD-50 (g/kg)				
	Applied to Skin	Taken by Mouth	Into Blood Stream	Beneath Skin	Into Body Cavity
Mouse	50	16.5-24.6	3.8-8.9	13.9-20.5	14.7-17.0
Rat	40	17.4-28.3	5.2-8.1	12.0-20.5	13.0
Guinea	-	11.0	-	-	5.5
Pig	-	14.0	-	-	-
Chicken	-	-	4.0	-	-
Cat	>11	10.0	2.5	-	-
Dog	>11	4.0	4.0	-	-
Monkey					

3 亚急性毒性

大量的监测显示,DMSO 不影响人类的肾功能。人类的监测及动物实验的研究显示,DMSO 有利尿作用,但无显著地肾损伤现象。动物实验报道,静脉注射 DMSO 有溶血现象。

4 慢性毒性

DMSO 经过大量的实验,不被认为是致癌剂。一项为期 18 个月的研究显示,猕猴口服 3300mg/kg/day,无毒性效应水平;口服或局部给予 DMSO 至 9g/kg/day 未发现肿瘤,骨髓涂片易正常^[9]。相当于人类(70KG)每天摄入 DMSO 210g,即 3g/kg/day。另一项研究显示 84 个人,局部给药 DMSO 2.8g/kg/day,连续给药 3 个月除了呼气有大蒜味,身体有味外,未发现 DMSO 相关的毒性反应。另外,38 人(平均年龄 21-55 岁)给予含 80%的 DMSO 凝胶(1g/kg/day)持续给药 12 周,未发现任何 DMSO 相关的反应^[10]。其他研究证实 DMSO 对狗,兔子,豚鼠,猪的眼睛的影响为种属特异性,未在灵长类动物身上

发现,包括人类^[11,12]。鉴于其安全性目前亦用于骨关节炎的治疗^[13]。

5 代谢产物毒性

DMSO 的代谢产物 DMSO₂ 及 DMS 存在于尿液和粪便中。DMS 具有大蒜味或者牡蛎味,主要经肾脏排泄,由尿中排出,无肾脏蓄积。DMSO 的代谢产物 DMSO₂ 少量存在于人类的尿液中^[14];DMS 亦自然存在于植物,大气,湖泊和海洋中^[15]。这两种代谢产物(DMSO₂,DMS)都容易从人体排出。因为他们在自然界广泛存在,而且容易降解和排出。所以,DMSO 可以用于食品生产,而不必担心于其毒性。

6 皮肤暴露

DMSO 比水对皮肤的渗透性更高。但由于其低毒性,同时不携带其他低渗透性物质通过皮肤吧,故而认为,皮肤暴露无显著性伤害。

7 吸入毒性

大鼠单次或者重复暴露于 DMSO 的气雾剂环境中,血液学和组织器官无改变^[16,17]。但是作为养成好的实验卫生习惯,建议减少在高浓度的 DMSO 气雾剂或者雾霾中暴露。

8 遗传毒性

DMSO 对沙漠菌属,果蝇属,鱼的细胞无致畸性,而且作为溶剂广泛用于致畸性的实验研究。虽然 DMSO 在 5-50%的浓度下具有抑菌或杀菌作用,但是仍不能证明 DMSO 有致染色体畸变的作用。长期给予猕猴 DMSO 未见致畸性^[9]。体内遗传学研究显示,给予大鼠腹腔内注射 DMSO 后股骨内出现许多异常的骨髓细胞^[18]。但是沙门氏菌属及其他毒理学研究,特别是畸形学的数据显示:异常的骨髓细胞是由于 DMSO 注射后的直接毒性,而非致畸性导致。有文献报道:职业暴露于 DMSO 40 年的工人未见致畸作用^[19]。

7 生殖发育毒性

致畸学研究显示:除非给予高剂量引起母源性损伤,或给予最大可耐受剂量,孕小鼠,大鼠,兔,豚鼠口服 DMSO 无致畸性。DMSO 在低剂量下无致畸性,并且与给药方式无关。综合考虑,其潜在致畸性与给药方式,剂量,孕期暴露时间有关,与斑马鱼胚胎暴露于 DMSO 的毒性研究的研究相一致^[20]。DMSO 不认为具有直接的胚胎毒性,已作为冷冻保护剂广泛用于保持哺乳动物的精子及干细胞^[19,21]。

参考文献(References)

- [1] Marks P.A, R. Breslow. Dimethyl sulfoxide to vorinostat: development of this histone deacetylase inhibitor as an anticancer drug [J]. Nat Biotechnol,2007,25(1):84-90
- [2] 黄波,龙颖,朱茂祥,等.烹调油烟冷凝物对细胞的氧化损伤及 DMSO 的保护作用[J]. 实用预防医学,2008,15(6):1733-1735
- Huang Bo, Long Ying, Zhu Mao-xiang, et al. Oxidative Damage of BEAS-2B Cell Induced by Cooking Oil Fume Condensation and Its Protection by DMSO [J]. Practical Preventive Medicine, 2008, 15(6): 1733-1735

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- [11] Zheng X, Lu J, Deng L, et al. Preparation and characterization of magnetic cationic liposome in gene delivery[J]. *Int J Pharm*, 2009,366(1-2):211-217
- [12] Mikhaylov G, Mikac U, Magaeva AA, et al. Ferri-liposomes as an MRI-visible drug-delivery system for targeting tumours and their microenvironment[J]. *Nat Nanotechnol*, 2011,6(9):594-602
- [13] Reimer P, Balzer T. Ferucarbotran (Resovist): a new clinically approved RES-specific contrast agent for contrast-enhanced MRI of the liver: properties, clinical development, and applications [J]. *Eur Radiol*, 2003,13(6):1266-1276
- [14] Dave SR, Gao X. Monodisperse magnetic nanoparticles for biodetection, imaging, and drug delivery: a versatile and evolving technology[J]. *Wiley Interdiscip Rev Nanomed Nanobiotechnol*, 2009,1(6):583-609
- [15] Sung MW, Yeh HC, Thung SN, et al. Intratumoral adenovirus-mediated suicide gene transfer for hepatic metastases from colorectal adenocarcinoma: results of a phase I clinical trial[J]. *Mol Ther*, 2001,4(3):182-191
- [16] Bhattarai SR, Kim SY, Jang KY, et al. N-hexanoyl chitosan-stabilized magnetic nanoparticles: enhancement of adenoviral-mediated gene expression both in vitro and in vivo [J]. *Nanomedicine*, 2008,4(2):146-154
- [17] Krotz F, de Wit C, Sohn HY, et al. Magnetofection--a highly efficient tool for antisense oligonucleotide delivery in vitro and in vivo[J]. *Mol Ther*, 2003,7(5 Pt 1):700-710
- [18] Muthana M, Scott SD, Farrow N, et al. A novel magnetic approach to enhance the efficacy of cell-based gene therapies[J]. *Gene Ther*, 2008,15(12):902-910
- [19] Fattahi H, Laurent S, Liu F, et al. Magnetoliposomes as multimodal contrast agents for molecular imaging and cancer nanotheragnostics [J]. *Nanomedicine (Lond)*, 2011,6(3):529-544
- [20] Wang F, Chen Y, Zhang D, et al. Folate-mediated targeted and intracellular delivery of paclitaxel using a novel deoxycholic acid-O-carboxymethylated chitosan-folic acid micelles [J]. *Int J Nanomedicine*, 2012,7:325-337
- [21] Yousefpour P, Atyabi F, Vasheghani-Farahani E, et al. Targeted delivery of doxorubicin-utilizing chitosan nanoparticles surface-functionalized with anti-Her2 trastuzumab [J]. *Int J Nanomedicine*, 2011,6:1977-1990

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- [3] 韩旭芳, 屠慧渭, 傅雅琴, 等. DMSO 对白血病肿瘤细胞 HL-60 增殖的影响[J]. 北京电力高等专科学校学报, 2010,10: 28
Han Xu-fang, Tu Hui-wei, Fu Ya-qin, et al. DMSO on HL-60 leukemia tumor cell proliferation [J]. *Beijing Electric Power College*, 2010,10:28
- [4] Kashino G, Liu Y, Suzuki M, et al. An alternative mechanism for radioprotection by dimethyl sulfoxide, possible facilitation of DNA double-strand break repair[J]. *Radiat Res*, 2010,51(6):733-740
- [5] Colucci, M, Maione, F, Bonito M. C, et al. New insights of dimethyl sulphoxide effects (DMSO) on experimental in vivo models of nociception and inflammation [J]. *Pharmacol Res*, 2008,57(6):419-425
- [6] Marks, P.A, R. Breslow. Dimethyl sulfoxide to vorinostat: development of this histone deacetylase inhibitor as an anticancer drug[J]. *Nat Biotechnol*, 2007,25(1):84-90
- [7] Eby WM, Tabatabai MA, Bursac Z. Hyperbolic modeling of tumor growth with a combined treatment of iodoacetate and dimethylsulphoxide[J]. *BMC Cancer*, 2010,10:509
- [8] Cona M, M, Li, J, Chen, F, et al. A safety study on single intravenous dose of tetrachloro-diphenyl glycoluril [iodogen] dissolved in dimethyl sulphoxide (DMSO)[J]. *Xenobiotica*, 2013,1(2):24-28
- [9] Vogin, E.E S.Carson, G. Cannon, et al. Linegar and L.F. Rubin. Chronic Toxicity of DMSO in Pri-mates [J]. *Toxicology and Applied Pharmacology*, 1970,16: 606-612
- [10] Hull, F.W, D.C. Wood, R.D. Brobyn. Eye Effects of DMSO: Report of Negative Results[J]. *Northwest Medicine*, 1969,1:39-41
- [11] Rengstorff RH, J.P. Petrali, V.M. Sim. Cataracts Induced in Guinea Pigs by Acetone, Cyclohexanone and Dimethyl Sulfoxide [J]. *American Journal Optometry*, 1972,49:308-319
- [12] de la Torre J.C., J.W. Sugeon T. Ernest, R. Wollman. Subacute Toxicity of Intravenous Dimethyl Sulfoxide in Rhesus Mon keys[J]. *Journal of Toxicology and Environmental Health*, 1981,7: 49-57
- [13] Brien S, Prescott P, Bashir N, et al. Systematic review of the nutritional supplements dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM) in the treatment of osteoarthritis[J]. *Osteoarthritis Cartilage*, 2008,16(11):1277-1288
- [14] Physicians' Desk Reference (PDR). 48th Edition. Medical Economics Data Production Company[J]. Mont vale, NJ, 1994:1842-1843
- [15] Pearson T.W, Dawson, H.J, Lackey H.B. Natural Occurring Levels of Dimethyl Sulfoxide in Selected Fruits, Vegetables, Grains, and Beverages[J]. *Agric Food Chem*, 1981,29:1089-1091
- [16] Inh A, Caujolle F, Caujolle-Meynier D, et al. Comparative Actions of Aerosols of Dimethyl Sulfoxide, Dimethyl Sulfoxide and Dimethyl Sulfone on the Isolated Lung of Guinea Pig: Re-lation Between Chemical Structure and Biologic Activity [J]. *Arch. Int. Pharmac*, 1964, 152:3-4
- [17] Inh. B. Uramura, T. An Experimental Study on the Toxicity of Dimethyl Sulfoxide Used as a Solvent [J]. *Igaku Ken Kyu*, 1961,30: 2235-2261
- [18] Kapp, R. W., Jr, B.E. Eventoff. Mutagenicity of Dimethyl Sulfoxide (DMSO): in vivo Cytogenetics Study in the Rat [J]. *Teratog Carcinog Mutagen*, 1980,1(2):141-145
- [19] Brayton C.F. Dimethyl Sulfoxide (DMSO): a review[J]. *Cornell Vet*, 1986, 6:61-90
- [20] Hallare A.V, H.R. Kohler, R. Triebksorn. Developmental toxicity and stress protein responses in zebrafish embryos after exposure to diclofenac and its solvent, DMSO [J]. *Chemosphere*, 2004,56(7): 659-666
- [21] Zhang, S. Yu, X. Chen, Z, et al. Viscosities of the ternary solution dimethyl sulfoxide/water/sodium chloride at subzero temperatures and their application in cryopreservation[J]. *Cryobiology*, 2013,66(2): 186-191