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亮丙瑞林药品不良反应文献分析

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摘要:目的 促进临床合理使用亮丙瑞林。**方法** 计算机检索中国期刊全文数据库(CNKI)、万方数据库及PubMed,Embase数据库,收集自建库起至2020年12月31日关于亮丙瑞林药品不良反应(ADR)的报道,对患者年龄、性别、原患疾病、使用药物、联合用药,ADR发生时间、分布、临床表现、治疗与转归等数据进行统计与分析。**结果** 共纳入86篇文献,涉及105例(147例次)患者。其中男性较多(56.19%),60岁以上患者较多(53.33%);原患疾病集中于前列腺癌(55.24%);多数使用亮丙瑞林长效制剂(103例),单次注射量为3.6～45.0 mg,用药频次为4周至6个月,用药方式为肌肉或皮下注射;与比卡鲁胺(7例)、氟他胺(7例)联合用药最多;多发生于用药后0.5～1年(17.01%);主要分布于注射部位(23.13%),临床表现为注射部位肉芽肿等;经药物对症治疗后好转或痊愈68例次。**结论** 亮丙瑞林ADR总体呈多样化。应加强对速发型ADR的观察和监测,做好对迟发型ADR的跟踪和随访,警惕可能发生的严重ADR,提升用药安全意识,确保临床用药安全。

关键词:亮丙瑞林;药品不良反应;文献分析;合理用药

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Adverse Drug Reactions Caused by Leuprorelin: A Literature Analysis

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Abstract: Objective To promote the rational use of leuprorelin in the clinic. **Methods** CNKI, WanFang database, PubMed and Embase database were searched from the inception to December 31, 2020 for collecting the case reports of adverse drug reactions (ADRs) caused by leuprorelin. The data of patients' age, gender, primary disease, drugs, combined medication, occurrence time, distribution, clinical manifestation, treatment and outcome of ADRs were statistically analyzed. **Results** A total of 86 studies were included, involving 105 patients (147 cases of ADRs), of which there were mainly male patients (56.19%) and patients over 60 years old (53.33%). ADRs were concentrated in primary disease of prostate cancer (55.24%). Most patients (103 cases) were treated with leuprorelin long－acting preparation, the single injection volume was 3.6－45.0 mg, the medication frequency was 4 weeks to 6 months, and the medication method was intramuscular or subcutaneous injection. The combination of leuprolide with bicalutamide (seven cases) and flutamide (seven cases) was the most. Most ADRs (17.01%) occurred within 0.5－1 year after medication, which were mainly distributed at the injection site (23.13%), and its clinical manifestations were granuloma at the injection site. A total of 68 cases of ADRs were improved or cured after symptomatic treatment. **Conclusion** ADRs caused by leuprorelin are generally diversified. In order to ensure clinical medication safety, we should strengthen the observation and monitoring of rapid－onset ADRs, do a good job in the tracking and follow－up of late－onset ADRs, be alert to possible severe ADRs, and improve the awareness of medication safety.

Key words: leuprorelin; adverse drug reactions; literature analysis; rational drug use

亮丙瑞林为人工合成的促黄体生成释放激素(LH－RH)的九肽类似物,通过作用于垂体特异性受体抑制垂体－性腺系统功能,减少促性腺激素的分泌和释放,还可降低睾丸和卵巢对促性腺激素的反应及睾酮、雌激素的生成,临床广泛用于治疗前列腺癌、子宫肌瘤或子宫内膜异位症、中枢性早熟等疾病,相关药品不良反应(ADR)的报道也较多,但不同人群的ADR表现差异较大,其特点尚待讨论。本研究中系统性地分析了国内外关于亮丙瑞林ADR的报道,探讨其发生规律及特点,为临床的合理应用提供参考。现报道如下。

1 资料与方法

1.1 检索策略

计算机检索中国期刊全文数据库(CNKI)、万方数据库及PubMed,Embase数据库,检索时限为各数据库自建库起至2020年12月31日。中文检索词为"亮丙瑞林""不良反应""副作用",英文检索词为"Leuprorelin""adverse reaction""side effect"等。

1.2 文献纳入与排除标准

纳入标准:不良反应个案报道;主要治疗药物为亮丙瑞林;符合不良反应相关判断标准。排除标准:重复

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或同源文献；二次文献；非中、英文文献；非全文文献。

1.3 资料提取

提取内容包括患者的年龄、性别、原患疾病，ADR 临床表现、发生时间、分布、治疗与转归等。

2 结果

2.1 总体情况

共检索出 2 225 篇文献，最终纳入 86 篇[1-86]，文献筛选流程及结果见图 1。共纳入 105 例患者，涉及亮丙瑞林 ADR 147 例次。

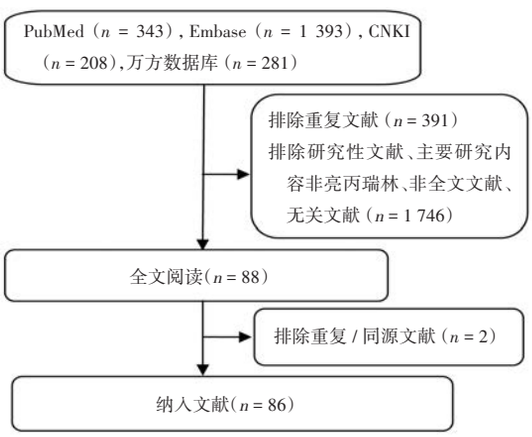

图 1 文献筛选流程

Fig. 1 Flow chart of literature screening

2.2 ADR 相关因素

性别与年龄：105 例患者中，男性较多（56.19%），60 岁以上患者较多（53.33%）。详见表 1。

表 1 ADR 报告中患者性别与年龄分布（n = 105）

Tab. 1 Distribution of patients′ gender and age in ADR reports（n = 105）

年龄	性别（男 / 女 / 不详，例）	小计（例）	占比（%）	年龄	性别（男 / 女 / 不详，例）	小计（例）	占比（%）
0~18 岁	0/13/3	16	15.24	60~79 岁	44/0/0	44	41.90
19~39 岁	1/19/0	20	19.05	≥80 岁	12/0/0	12	11.43
40~59 岁	2/11/0	13	12.38	合计	59/43/3	105	100.00

原患疾病：105 例患者中，原患前列腺癌占比最大（55.24%），其次为子宫内膜异位症（15.24%）。详见表 2。

表 2 ADR 报告中患者原患疾病分布（n = 105）

Tab. 2 Distribution of patients′ primary diseases in ADR reports（n = 105）

原患疾病	例数	占比（%）	原患疾病	例数	占比（%）
前列腺癌	58	55.24	不孕症及人工辅助生殖	4	3.81
子宫内膜异位症	16	15.24	乳腺癌	2	1.90
性早熟	15	14.29	子宫纤维瘤	1	0.95
子宫肌瘤	8	7.62	不详	1	0.95

使用药物与联合用药：105 例患者中，1 例每日注射短效亮丙瑞林制剂；1 例先后使用短、长效亮丙瑞林制剂，其余患者均使用亮丙瑞林长效制剂；19 例药品使用方法不详，其余患者单次注射量为 3.6 ~ 45.0 mg，用药频次为 4 周至 6 个月，用药方式为肌肉或皮下注射。30 例存在联合用药，其中与比卡鲁胺（7 例）、氟他胺（7 例）合用最多。

发生时间：105 例（147 例次）患者中，16 例 ADR 发生在注射后 24 h 内（10.88%），包括垂体卒中、药物热、肉芽肿等。其中垂体卒中 5 例，发生时间为从注射后 10 min 至数小时；过敏性休克 4 例，均于注射后 30 min 内发生，其中 1 例为第 2 次注射时发生。9 例在用药 2 年后发生（6.12%），包括股骨滑脱、脂肪肝、肝药酶升高等。详见表 3。

表 3 ADR 发生时间分布（n = 147）

Tab. 3 Distribution of the occurrence time of ADRs（n = 147）

发生时间	例次	构成比（%）	发生时间	例次	构成比（%）
24 h 内	16	10.88	4~6 个月	12	8.16
1~7 d	16	10.88	0.5~1 年	25	17.01
1~4 周	24	16.33	1~2 年	4	2.72
1~2 个月	24	16.33	超过 2 年	9	6.12
2~4 个月	8	5.44	不详	9	6.12

临床表现：105 例患者中，注射部位分布最多（23.13%），主要表现为注射部位肉芽肿或无菌性脓肿；其次为神经部位（16.33%）。详见表 4。

2.3 ADR 治疗与转归

105 例（147 例次）患者的 ADR 报告中，3 例次死亡，分别由于 Gn-RH 激动剂相关的黏液水肿继发的胰腺炎、子宫内膜腺癌、多器官衰竭；37 例次停药后自行恢复；68 例次药物对症治疗后好转或痊愈；22 例次手术对症治疗后痊愈；17 例次结局不详。

3 讨论

全文共纳入 86 篇文献，其中 1 篇文献中 3 例儿童患者的性别不详，1 篇文献报道 1 例患者无原患疾病，5 篇文献中 7 例患者未提及 ADR 发生的具体时间。约 54.4% 的 ADR 发生在用药后 2 个月内，存在相对合理的时间关系。ADR 主要涉及注射部位损害、神经紊乱、中枢及外周神经系统损害、皮肤及其附件损害等，与亮丙瑞林市售制剂说明书中已知的 ADR 分布一致。停药或减量后，25.2% 的患者 ADR 消失或减轻，61.2% 的患者经对症治疗后好转或痊愈，3 例患者再次使用该药物时出现相同的 ADR，这说明该 ADR 的发生与亮丙瑞林相关性较强。老年患者常合并基础疾病，应加强对 ADR 的监测，避免严重 ADR 发生，且亮丙瑞林 ADR 与剂量相关性可能不强。

亮丙瑞林在国内获批的适应证主要有子宫内膜异位症、子宫肌瘤、雌激素受体阳性的绝经前乳腺癌、前列腺癌和中枢性性早熟症。本研究中约 3.81% 的患者

表4 ADR累及器官/系统及其临床表现（n = 147）

Tab. 4 Organs/systems involved in ADRs and their clinical manifestations（n = 147）

累及器官/系统	例次/占比(%)	临床表现(例次)
注射部位损害	34/23.13	注射部位肉芽肿(22)、注射部位红斑(2)、注射部位硬结(2)、注射部位无菌性脓肿(8)
神经紊乱	24/16.33	睡眠障碍(5)、躁狂反应(5)、偏执(2)、焦虑(2)、抑郁(4)、自杀企图(2)、精神病发作(1)、情绪不稳定(2)、幻觉(1)
中枢及外周神经系统损害	15/10.20	头痛(2)、头晕(1)、垂体卒中(5)、良性垂体瘤(1)、脑病(1)、脑脊液鼻漏(1)、昏迷(1)、感觉异常(1)、尿潴留(1)、锥体外系病(1)
皮肤及其附件损害	10/6.80	皮疹(4)、荨麻疹(4)、多汗(1)、银屑病(1)
全身性损害	9/6.12	过敏性休克(4)、水肿(1)、发热(1)、死亡(3)
呼吸系统损害	8/5.44	间质性肺炎(5)、呼吸困难(2)、气胸(1)
肌肉骨骼系统损害	7/4.76	股骨滑脱(3)、医源性肌病(1)、肌无力(2)、关节痛(1)
代谢与营养障碍	6/4.08	脂代谢病(1)、碱性磷酸酶升高(1)、高血糖(4)
心外血管损害	4/2.72	紫癜(2)、深静脉血栓(1)、脑梗死(1)
女性生殖系统损害	4/2.72	子宫肌瘤坏死(1)、子宫内膜癌(1)、子宫附件扭转(1)、卵巢过度刺激(1)
肝胆系统损害	4/2.72	肝功能异常(1)、传染性肝炎(1)、脂肪肝(1)、胆汁淤积型肝炎(1)
胃肠系统损害	4/2.72	肠道穿孔(1)、肠梗阻(1)、胰腺炎(1)、胃酸过多(1)
心血管系统一般损害	3/2.04	冠状动脉剥离(1)、心脏病(2)
肿瘤	3/2.04	脑膜瘤(2)、鳞状细胞癌(1)
胶原组织损害	3/2.04	变态性脉管炎(1)、红斑狼疮综合征加剧(2)
视觉损害	3/2.04	视觉异常(1)、视神经乳头水肿(2)
交感/副交感神经损伤	2/1.36	潮红(2)
内分泌紊乱	2/1.36	黏液性水肿(1)、甲状腺炎(1)
泌尿系统损害	1/0.68	肾功能异常(1)
红细胞异常	1/0.68	贫血(1)

因人工辅助生殖使用亮丙瑞林，由于其可促进卵泡发育，提高人工辅助生殖妊娠率，并可有效降低卵巢过度刺激综合征的发生[87]，但目前在国内仍属超药品说明书用药，由于亮丙瑞林在动物实验中被证实可能导致胎儿骨骼形成异常，因此建议医师在使用前应充分排除患者妊娠，并在严密监测ADR的情况下使用。

过敏性休克4例，均发生在注射后30 min内，其中3例在首次注射后，1例在首次注射后仅存在皮肤轻度反应，第2次注射后30 min内发生过敏性休克，提示在既往未发生过敏反应的患者中也可能发生过敏性休克等严重速发型过敏反应。4例患者及时予肾上腺素、糖皮质激素治疗后均痊愈，无死亡情况发生。提示在制订治疗方案时，应详细了解患者的过敏史，建议在应用亮丙瑞林后30 min以内加强用药监护。如发生过敏，应及时予肾上腺素抗过敏与支持治疗，避免严重ADR发生。

亮丙瑞林相关ADR涉及的身体系统较广泛，注射部位肉芽肿和无菌性脓肿是出现频率较高的临床表现。亮丙瑞林作为一种水溶性多肽类药物，易被胃肠道中消化酶降解失活，不宜口服给药，且不易透过生物膜，于鼻腔等黏膜给药的生物利用度极低，在用于治疗多种激素依赖性疾病时，需较长疗程，目前临床应用大多为缓释微球制剂，其可避免频繁注射，通常1～6个月注射1次即可。但缓释制剂引发的注射部位肉芽肿和无菌性脓肿多有报道，且再次注射可重复发生。亮丙瑞林微球制剂中辅料包括共聚物（聚乳酸、丙交酯乙交酯）、*D*－甘露醇、羧甲基纤维素钠、表面活性剂（吐温80），不排除因辅料中高分子物质引起巨噬细胞参与免疫应答，从而引起结节状病灶或炎性反应，形成无菌脓肿或肉芽肿。据报道，通过使用多磺酸粘多糖局部涂抹，可有效预防亮丙瑞林引发的皮肤脓肿反应[88]，其中8例无菌性脓肿患者均为儿童，提示使用亮丙瑞林缓释制剂时，如产生硬结、肿物或红肿，尤其是儿童患者，应及时就诊，必要时还可换用曲普瑞林注射液等；神经紊乱也是亮丙瑞林发生率较高的ADR，因此患有精神系统疾病或睡眠障碍的患者在使用亮丙瑞林时，要重点监护其精神症状，如抑郁、狂躁等，必要时更换替代药品或予药物对症治疗。

作为治疗中枢性性早熟的有效药物，亮丙瑞林可应用于2岁以上儿童，其可通过抑制下丘脑－垂体－性腺轴减少性激素分泌，减缓中枢性性早熟患儿的骨龄进展，增加成年后的身高。16例患儿中，报道了3例股骨滑脱的ADR，发生于2.15～6.75年，表现为跛行、髋关节疼痛等，经手术治疗后预后均良好。这类患者用药周期较长，居家用药过程中ADR易被忽略。虽Gn－RH治疗一般对人体长期峰值骨量和骨密度无影响，但骨骺板的雌激素刺激减少和骨代谢的短暂变化，可能是导致股骨滑脱的重要原因。虽然这种认识是一种假设，但儿科医师开具处方时应关注并监测此ADR，定期回访，如发生跛行和髋关节疼痛，应注意识别，并及时给予相应治疗。

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