药物不良反应
Adverse Drug Reactions

# 31 例米托坦药物不良反应的分析

## Analysis of adverse drug reactions of mitotane in 31 patients

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**摘要: 目的**　分析肾上腺皮质癌患者服用米托坦所致药物不良反应(ADR)的发生特点。**方法**　对2019年6月至2021年6月北京协和医院服用米托坦的肾上腺皮质癌患者进行药学监护，监测米托坦相关ADR，对ADR发生时患者的性别、年龄、用药日剂量及频率、用药累积剂量、累及器官/系统、ADR转归等进行统计分析。**结果**　本院共有43例肾上腺皮质癌患者服用米托坦，其中31例患者服药后发生米托坦相关ADR，ADR发生率为72.09%，其中女性患者多于男性，以31～60岁的患者居多；3例严重ADR患者血药浓度均超出治疗窗；ADR可累及多个系统/器官，最常发生于消化系统和神经系统；大多数ADR在对症治疗、减量或停药后得到改善。**结论**　米托坦ADR多且发生率高，临床应定期监测米托坦引起的ADR，通过血药浓度监测调整给药剂量，并给予适当治疗措施，以确保患者用药安全。
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**Abstract: Objective**　To analyze the characteristics of adverse drug reactions (ADRs) caused by mitotane in patients with adrenocortical carcinoma. **Methods**　From June 2019 to June 2021, the patients with adrenocortical carcinoma who received mitotane in Peking Union Medical College Hospital were under pharmaceutical care, focusing on monitoring mitotane－related ADRs. The gender, age, daily dosage, administration frequency, cumulative dose, organ or system involvement, and outcome of adverse drug reactions of patients were statistically analyzed. **Results**　Among 43 ACC patients with mitotane, 31 patients developed mitotane－related ADRs after taking the drug, and the ADRs incidence rate was 72.09%, of which more female than male, most of whom were 31－60 years old. The concentration of mitotane in 3 patients with severe ADRs all exceeded the treatment range. ADRs involved multiple systems and organs, most often occurred in the digestion system and nervous system. Besides, most ADRs were improved after symptomatic treatment, dose reduction, or discontinuation. **Conclusion**　Mitotane has many ADRs with a high incidence. The adverse reactions caused by mitotane should be monitored regularly. The dosage should be adjusted through blood concentration monitoring, and appropriate treatment measures should be given to ensure the safety of patients' medication.
**Key words:** mitotane; adverse drug reaction; rational drug use

肾上腺皮质癌(Adrenocortical Carcinoma,ACC)是一种发病率极低(0.5~2.0例/百万),预后极差的内分泌恶性肿瘤[1]。对于晚期或有全身复发的,以及行根治性手术后辅助化疗的ACC患者,米托坦片是目前指南推荐药物[2-3]。米托坦是唯一被美国食品药品监督管理局批准用于治疗ACC的细胞毒性药物,其主要通过抑制肾上腺皮质类固醇的合成来诱导肿瘤细胞的死亡[4]。于2019-03-28,国家药品监督管理局药品评审中心发布《关于第二批临床急需境外新药的公示》并附临床急需境外新药名单(第2批),米托坦位列其中。2019年6月,北京协和医院采用一次性进口方式首次将米托坦引入国内。本文对我院2019年6月至2021年6月间ACC患者口服米托坦后药物不良反应(Adverse Drug Reaction,ADR)进行统计,通过分析ADR的发生特点,为临床安全用药提供参考。

## 资料与方法

### 1 资料来源

收集2019年6月至2021年6月收治的应用米托坦后出现ADR患者的病例资料。

入选标准 米托坦ADR信息完整,符合ADR判断标准。

排除标准 ADR描述不清或者相关信息不完整或重复。

### 2 研究方法与内容

采集患者达稳后静脉血,用高效液相法测定血中米托坦谷浓度[5]。

统计ADR发生时,患者的性别、年龄、用药日剂量及频率、用药累积剂量等信息。ADR的因果关系评价按照我国ADR监测中心制定的判断标准分析确定。依据常见不良事件评价标准(Common Terminology Criteria for Adverse Events,CTCAE)评估ADR严重性,并将3,4级ADR定义为严重ADR。

### 3 统计学处理

用SPSS 25.0软件进行统计分析。计量资料符合正态分布用 $\bar{x} \pm s$ 表示,不符合正态分布则以中位数和四分位数表示,比较用独立样本 $t$ 检验;计数资料用率表示,比较用 $\chi^2$ 检验。

## 结 果

### 1 一般资料

2019-2021年共有43例ACC患者服用米托坦,男性18例,女性25例,其中31例(72.09%)发生米托坦相关ADR,严重ADR共3例(9.68%),均表现为3级中枢神经系统ADR(严重,但是没有生命危险)。31例中共有男性12例(38.71%),ADR发生率66.67%,女性19例(61.29%),ADR发生率76.00%,女性ADR发生率略高于男性,但差异无统计学意义($P>0.05$);患者平均年龄(47±10)岁,年龄分布28~72岁,其中以31~60岁为主,见表1。

### 2 ADR发生时的给药日剂量和频率

在31例发生ADR的患者中,给药日剂量2.0~2.9 g·d$^{-1}$占比最多,共20例(64.52%)。不同给药频率组间ADR的报告例数差异无统计学意义($P>0.05$),每日给药4次的ADR报告较少,共7例(占22.58%),见表2。

### 3 ADR发生时的给药累积剂量

31例ACC患者米托坦累积剂量中位值为300.0(180.0~730.0)g。米托坦累积剂量<300.0 g及≥300.0 g的2组患者中,ADR发生率分别为64.28%(14例ACC患者中9例ADR)和75.86%(29例ACC患者中22例ADR),差异无统计学意义($P>0.05$)。米托坦血药浓度参考值范围为14~20 mg·L$^{-1}$[2,6],3例严重ADR患者累积剂量分别为290,900和1 155 g,对应的血药浓度分别为42.8,25.3和29.9 mg·L$^{-1}$,均超出正常范围。

### 4 ADR累及器官/系统及主要临床表现

在31例ADR患者中,由于1例ADR可能涉及几种不同的ADR,分别统计后累计124例次ADR。米托坦ADR涉及多个系统,以消化系统异常最为常见,共24例(77.42%);其他常见ADR依次是中枢神经异常

**表1 发生药物不良反应(ADR)患者的年龄分布**

**Table 1** Age distribution of adverse drug reaction (ADR) cases

| Age(year) | <30 | 31-40 | 41-50 | 51-60 | >60 |
|---|---|---|---|---|---|
| *n*(Male/Female) | 0/1 | 3/6 | 2/6 | 5/6 | 2/0 |
| Percentage(%) | 3.23 | 29.03 | 25.81 | 35.48 | 6.45 |

**表2 发生ADR时患者给药日剂量和频率**

**Table 2** Drug daily dosage and administration frequency of ADR cases

| Daily dosage (g·d$^{-1}$) | Administration frequency (*n*) | | | Value (*n*,%) |
|---|---|---|---|---|
| | *bid* | *tid* | *qid* | |
| 1.0-1.9 | 1 | 4 | 0 | 5(16.13) |
| 2.0-2.9 | 11 | 3 | 6 | 20(64.52) |
| 3.0-4.0 | 1 | 4 | 1 | 6(19.35) |
| Total | 13 | 11 | 7 | 31(100.00) |

**表 3** ADR 累及系统或器官及临床表现

**Table 3** System – organ class involved in ADR and clinical manifestations

| System – organ class | Clinical manifestation | Value( *n*,% ) |
|---|---|---|
| Digestive system | Anorexia( 12) ,nausea( 20) ,vomiting( 13) ,diarrhea( 11) | 24( 77. 42) |
| Nervous system | Depression( 4) ,dizziness or vertigo( 14) ,mental disorder or weakness( 9) | 14( 45. 16) |
| Liver | Increased liver enzyme | 13( 41. 94) |
| Endocrine system | Male breast development( 7) ,hypothyroidism( 2) ,decreased free testosterone in male( 2) | 9( 29. 03) |
| Skin | Rash( 5) | 5( 16. 13) |
| Locomotor system | Motor and coordination dysfunction( 5) | 5( 16. 13) |
| Metabolic system | Hypercholesterolemia( 2) ,hypertriglyceridemia( 1) | 2( 6. 45) |
| Hemic and lymphatic system | Leukopenia( 1) | 1( 3. 23) |
| Other | Macular lesions( 1) ,hemorrhagic cystitis( 1) ,fever( 1) | 3( 9. 68) |

*: A case of ADR may involve several different ADRs, and the statistics are based on the number of patients

和肝酶升高,分别为 14 例( 45. 16%) 和 13 例( 41. 94%) ,见表 3。

**5 ADR 发生后的处置和预后**

在 31 例 ADR 患者中,共有 26 例( 83. 87%) 进行了对症治疗或者减少药物剂量,其中 6 例( 19. 35%) 同时对症治疗和减量处理,患者症状均好转或耐受; 3 例( 6. 98%) 严重 ADR 患者进行了停药处理,待症状好转后,分别在停药 2,4,5 个月后再次服药; 2 例( 6. 45%) 结果不明。

## 讨 论

在 43 例口服米托坦的 ACC 患者中,31 例发生 ADR,其中女性患者以及 31 ~ 60 岁患者 ADR 发生率更高,这可能与 ACC 在女性以及 40 ~ 60 岁人群中患病率更高相关[7-8]。不同给药日剂量、给药频率及累积剂量间 ADR 报告数差异无统计学意义,提示对 ADR 发生率的影响可能较小。但值得注意的是,不同给药累积剂量间 ADR 无显著性差异,但均导致严重 ADR 的发生。米托坦推荐治疗范围为 14 ~ 20 mg·L$^{-1}$,经检测后发现,3 例发生严重 ADR 患者的血药浓度均高于 20 mg·L$^{-1}$。研究发现,米托坦浓度受药物代谢酶细胞色素 P450 2B6( Cytochrome P450 2B6,*CYP2B6*) 基因多态性的影响,这可能用于解释即使在低累积剂量下,米托坦血药浓度仍可能超过正常范围,增加严重 ADR 发生的可能性[9]。这提示监测血浆米托坦浓度以指导剂量调整可能是控制严重 ADR 的关键因素。

在 31 例发生 ADR 患者中,24 例患者服用米托坦后出现胃肠道相关 ADR,其主要症状为厌食、恶心、呕吐和腹泻。不同于其他器官或系统相关 ADR 受米托坦血药浓度的影响,研究显示,胃肠道症状似乎与口服剂量更相关,并且主要发生在治疗初期[10]。在多数情况下,胃肠道症状较轻,通常在对症治疗后消退,大多数患者不需要停止服用药物。神经系统相关 ADR 是导致 ACC 患者停服米托坦最主要的原因。在 31 例发生 ADR 患者中,14 例患者出现神经系统相关 ADR,主要表现为抑郁、头晕或眩晕、精神障碍或虚弱。一些研究和个案报道显示,当血浆米托坦浓度为 >20 mg·L$^{-1}$时,与中枢神经系统相关的不良事件更频繁发生[11-13]。有研究指出,在中枢神经系统 ADR 3 级( 严重,但是没有生命危险) 或 4 级( 致命) 时,应停用米托坦,直到症状显著改善[2,14]。

除发生率较高的胃肠道和神经症状以及肝酶升高外,米托坦还会导致类似中央性甲状腺功能减退的临床表现,提示需要对患者甲状腺激素状态进行定期评估,并考虑用左旋甲状腺素替代治疗[15-16]。对于出现男性乳房发育症、血液游离睾酮减少等有性腺功能减退迹象的男性,建议评估睾酮和性激素结合球蛋白水平,并考虑补充睾酮[10]。虽然 31 例发生 ADR 患者中仅观察到 2 例高胆固醇血症,但在多项临床研究中,均显示在米托坦治疗期间胆固醇水平的升高,这可能与米托坦增加血中低密度及高密度脂蛋白成分有关[17-18]。鉴于米托坦是强 CYP3A4 诱导药,建议使用非 CYP3A4 代谢的普伐他汀和瑞舒伐他汀进行治疗[19-20]。

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