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哺乳期高血壓藥物的選擇

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摘　要

母乳是新生兒最好的食物，不論在營養成長、免疫調節功能方面，皆優於所有的人工配方製品，又兼有提升母子情感的好處，故母乳是出生後新生兒的最佳選擇。然而有些母親因妊娠前或妊娠時有高血壓，致使哺乳時仍需高血壓藥物的治療，考慮到對新生兒的影響，通常需轉換高血壓藥物。本文整理近年來的研究報告，主要透過高血壓藥物於乳汁中的分泌情形，探討藥物對哺乳期的影響，以及可能對新生兒的副作用，希望藉此選擇出對母親及新生兒最適合的降血壓藥物。在眾多降血壓藥物中，因利尿劑會抑制泌乳的特性，應避免哺乳期使用。就目前的資料來看，methyldopa、乙型阻抗劑有高血漿蛋白結合度 (如 propranolol)、captopril、enalapril 及部分鈣離子阻抗劑似乎是哺乳期有高血壓母親的安全治療法。另外，服藥後 3 至 4 小時再哺乳及緩慢增加藥量更可使藥物對新生兒的影響減至最小。

關鍵詞：高血壓藥物 (Antihypertensive agents)
哺乳 (Breastfeeding)
乳汁分泌 (Lactation)
高血壓 (Hypertension)

前言

在美國20-54 歲年紀的女性中，約有14% 的人有高血壓[1]，台灣的比例雖較低，但也相當接近。這些女性不但在懷孕期需要治療高血壓，哺乳期也是需要的。由於許多藥物會經由母體分泌到乳汁，故詳細了解高血壓藥物乳汁的分泌情形及對新生兒的影響是非常重要的。然而，關於高血壓藥物對新生兒的安全性之研究非常少，故本文著重於藉由整理各項高血壓藥物乳汁分泌量的分析，來選擇對新生兒影響最少的藥物。

乳汁中藥物濃度受到血漿蛋白結合度 (plasma protein binding)，酸鹼度 (acid base characteristics)，脂溶性 (lipid solubility) 及母親血中藥物濃度 (maternal serum concentration) 的影響。在這之中，血漿蛋白結合度是最重要的因素，越高血漿蛋白結合度的藥物越不容易分泌至乳汁[2]。乳汁因較血漿酸性，故較鹼性的藥物較可能分泌

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至乳汁中。母乳也含較多脂肪，故高脂溶性的藥物也較容易分泌至乳汁中[3]。另外，分子量越小的藥物也越容易在乳汁中出現[4]。除了這些因素外，新生兒體內藥物濃度與清除率、哺乳吸允的形式、母乳的組成、藥物的半衰期、哺餵的時間及母體內的藥物濃度也都息息相關。

據Wojnar的研究，早產兒體內藥物的清除率約只有母親的10%，足月的新生兒約有33%，而6個月大時約接近母親。至於母乳的組成，其中最重要的是脂肪含量，通常隨著時間的進行，母乳中的脂肪含量會漸高且越偏鹼性[5]。而哺乳與母親服藥時間間隔越長(尤其短效性藥物)，新生兒攝取的藥物濃度就越低。

Maternal milk to plasma ratio (M/P ratio)

由於影響的因素眾多，測量母乳對血漿的藥物濃度比值(maternal milk to plasma ratio) 似乎是一項簡單的方法及指標，我們可由此推算，在哺乳成分及量固定下，M/P ratio越高就代表新生兒暴露的劑量越多，也代表可能引起作用的機會越大。Kate等人分析1966至1988年四大類高血壓藥物的M/P ratio (見表一)[6]，此四類藥物爲乙型阻抗劑 (Beta blockers)，鈣離子阻抗劑 (calcium channel blockers)，血管加壓素轉化酶抑制劑 (angiotensin-converting enzyme (ACE) inhibitors) 及methyldopa。利尿劑因會抑制泌乳故不適用於哺乳而排除在外。並將M/P ratio分級成High (＞1)，Intermediate (0.5-1.0)，low (0.1-0.5) and negligible (＜0.1)，在大部份的研究中，M/P ratio是測量母親血中藥物的最大濃度與對應時間乳汁中的藥物濃度比。

討論

基於人道與倫理的考量，此類研究及個案皆不多，但仍可看出乙型阻抗劑 (Beta blockers) 及鈣離子阻抗劑 (calcium channel blockers) 在乳汁中的濃度隨著個別藥物有極大差異，無法一概而論，而血管加壓素轉化酶抑制劑 (ACE inhibitors) 卻都很一致的有negligible M/P ratio。Methyldopa雖然是一種在妊娠期高血壓的常用藥物，但關於此藥的研究卻很少，而且M/P ratio都不高。以下針對個別藥物討論。

一、乙型阻抗劑 (Beta blockers)[7]

乙型阻抗劑是最常在哺乳期被研究的藥物，它們皆爲弱鹼性，但因脂溶性及血漿蛋白結合度能力不同造成M/P ratio差距很大。

Metoprolol，nadolol，acebutalol，sotalol

表一：Number of subjects on antihypertensive medications with high, intermediate, and low M/P ratio

Medication	Total Sample size	High M/P ＞1.0	Intermediate M/P 0.5-1.0	Low M/P 0.1-0.5	Negligible M/P ＜0.1	Reference
Beta blockers						
Metoprolol	23	21	1	1	-	(19-22)
Nadolol	12	12	-	-	-	(23)
Acebutolol	7	7	-	-	-	(9)
Atenolol	7	7	-	-	-	(24-26)
Sotalol	17	14	2	1	-	(20,22,27,28)
Timolol	13	6	3	4	-	(29)
Labetalol	3	2	1	-	-	(10)
Propranolol	13	1	8	4	-	(28,30-34)
Ca channel blockers						
Diltiazem	1	1	-	-	-	(35)
Verapamil	1	-	1	-	-	(36)
Nimodipine	5	1	1	3	-	(37)
Nifedipine	2	-	-	2	-	(38,39)
ACE inhibitors						
Enalapril	9	-	-	1	8	(40-42)
Captopril	11	-	-	-	11	(43)
Methyldopa	8	-	2	5	1	(17,18,44)

and atenolol有著high M/P ratio，這表示它們可自由地分泌至乳汁中及被新生兒攝取，雖然如此，但卻只有2個個案報告新生兒發生心律不整[8,9]，大部分的研究仍認爲它們對新生兒來說是安全的。這是因爲新生兒攝取的劑量，若以每日1000ml母乳量計算，仍較治療劑量低許多，且大多數研究測量新生兒血中的藥物濃度，發現除了atenolol[8]及labetalol[10]外，其餘皆非常低或測不到。即使如此，仍應密切監測交感神經阻抗(adrenergic block)的症狀(如呼吸抑制、低血糖、嗜睡、心搏過慢等)。

相反地，mepidolol及propranolol有較低的M/P ratio，代表它們對哺乳來說是較安全的，尤其在母親或新生兒有肝腎功能受損時，更是優先考慮的藥物。

二、鈣離子阻抗劑(Calcium channel blockers)[11]

Dihydropyridine (DHP)類的verapamil之M/P ratio雖爲intermediate，有研究顯示哺餵的新生兒血中並無法測到verapamil，故認爲對新生兒影響小[12,13]。而diltiazem有著high M/P ratio，由於無不良反應報告過，目前認爲是安全的。至於Non-DHP類中，nifedipine分泌至乳汁地濃度低，一般認爲安全[14]。Nimodipine及Nicardipine分泌至乳汁的情形明顯，故不建議使用[15]。因爲無amlodipine和felodipine的研究或個案報告，也不建議使用。

三、血管加壓素轉化酶抑制劑(ACE inhibitors)[16]

在眾多的降壓藥當中，血管加壓素轉化酶抑制劑(ACE inhibitors)有著最低的M/P ratio。有研究顯示，在母親血液中血管加壓素轉化酶活性被明顯抑制的情況下，母乳中的血管加壓素轉化酶活性仍然是正常的，且短效的血管加壓素轉化酶抑制劑從無不良反應被報告過，這些皆顯示血管加壓素轉化酶抑制劑(ACE inhibitors)可能是哺乳期間最安全的降血壓藥物。

四、血管加壓素受體抑制劑(Angiotensin II receptor blockers)[16]

由於這類藥物出現較晚，在人體上試驗數據相當有限，故應衡量母親的利益及新生兒的可能危險後再謹慎使用。

五、Methyldopa[17,18]

雖然研究數目不多，但從哺餵的新生兒尿液及血漿中測出的methyldopa濃度皆不高，且無任何不良反應報告，故至今認爲它對哺乳是安全的。

六、Hydralazine[16]

據Liedholm等人的研究，hydralazine雖會分泌至乳汁中，但卻不會引起新生兒臨床相關症狀。

結論

對有高血壓又需哺乳的女性來說，高血壓藥物的選擇是個大問題，乳汁中藥物濃度是個很好

表二：Recommendation of American Academy of Pediatrics for Antihypertensive medications during Breastfeeding[14]

Medication	Recommendation
Beta blocker	
Metoprolol	Compatible with breastfeeding
Atenolol	Safer alternatives over atenolol should be used
Propranolol	Safe
Nadolol	Compatible with breastfeeding but should be monitored for adverse effect
Sotalol	Compatible with breastfeeding
Ca channel blocker	
Nifedipine	Safe
Amlodipine	Should not be used
Nicardipine	Not recommended
Verapamil	Compatible with breastfeeding
Diltiazem	Safe
ACE inhibitor	
Captopril	Compatible with breastfeeding
Enalapril	Safe
Fosinopril	Not recommended

的指標，可影響的因素有血漿蛋白結合度 (plasma protein binding)，酸鹼度 (acid base characteristics)，脂溶性 (lipid solubility)，及母乳的組成。在選擇藥物上，因利尿劑會抑制泌乳的特性，應避免哺乳期使用。就目前的資料來看，methyldopa 、乙型阻抗劑有高血漿蛋白結合度 (如propranolol)、captopril 、enalapril 及部分鈣離子阻抗劑似乎是哺乳期有高血壓母親的安全治療法。另外，服藥後3 至4 小時再哺乳及緩慢增加藥量更可使藥物對新生兒的影響減至最小。最後本文整理American Academy of Pediatrics 對哺乳期高血壓藥物的建議，見表二。

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Choice of Antihypertensive Agents During Lactation

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Approximately 14% of women 20-54 years of age have hypertension. Some of these women need antihypertensive treatment postpartum, and wish to breastfeed. Many drugs taken by the mother eventually appear in human milk. The drug level in milk depends on the physiochemical properties of the drug, the degree of plasma protein binding, acid-base characteristics, lipid solubility and the maternal serum concentration. Both the clinician and the mother have to weigh the risk to benefit ratio when maternal medication is prescribed. This article discusses the antihypertensive medication with regard to lactation by the maternal milk to plasma（M/P）ratios and indicates the choice of agents for the mother and infants. It seems reasonable to avoid diuretics, because of their potential to suppress lactation. By the available data to date, Methyldopa, beta blocker with high plasma protein binding（ex propranolol）, captopril, enalapril, and some calcium channel blockers are safe treatments of hypertension in a nursing mother, especially with slowly increasing dose and feeding 3-4 hours after taking antihypertensive medicine.（J Intern Med Taiwan 2007; 18: 115-119）