招待講演

「Differential mechanisms of antinociception induced by m, e and k opioids」

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特別講演

「がん疼痛緩和と医療用麻薬の適正使用について」

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Differential mechanisms of antinociception induced by ε-, μ-, and κ-opioid receptor agonists

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Opioid receptors can be classified into at least 4 types, ε-, μ-, δ-, and κ-opioid receptors. Stimulation of any one of these opioid receptors produce antinociception. Antinociception can be produced by either stimulation of opioid receptors at the spinal cord by administration of opioids directly to the spinal cord or by activation of descending pain control systems by application of opioid at the supraspinal sites. The descending pain control systems activated by various opioid receptor agonists involve multiple descending neural pathways and utilize different neurotransmitter systems. The descending pain control systems can be classified at least into ε opioid receptor mediated, μ opioid receptor mediated and κ opioid receptor mediated descending systems. The ε system is activated by β-endorphin, an ε receptor agonist, and the antinociception is mediated by the release of [Met^5]-enkephalin and the subsequent stimulation of opioid δ receptor in the spinal cord. The μ system is stimulated by morphine or DAMGO, μ receptor agonists, and the antinociception is mediated by the activation of spinipetal serotonergic and noradrenergic systems and stimulation of 5-HT receptors and α_2-adrenoceptors in the spinal cord. The κ system is activated by U50,488H, bremazocine or κ receptor agonists, and the antinociception is mediated by the release of 5-HT and dynorphin A [1-17] and stimulation of 5-HT receptor and κ receptors in the spinal cord.

Table 1 lists the selective opioid receptor agonists and antagonist used in our studies which selective stimulate or block the respective receptors. The experiments were mainly performed in mice using the tail-flick and hot-plate tests. The antinociception induced by β-endorphin given i.c.v. is blocked by i.c.v. administration of β-endorphin-[1-27], a selective ε opioid receptor antagonist, but not by CTOP or β-funaltrexamine, selective μ-opioid receptor antagonists,

naltrindole, a δ_2 opioid receptor antagonist, BNTX, δ_1-opioid receptor antagonist or nor-binaltorphine, a κ-opioid receptor antagonist. On the other hand, the antinociception induced by morphine or DAMGO, μ agonists, given i.c.v. is blocked by i.c.v. CTOP or β-funaltrexamine, but not by other ε, δ, or κ opioid receptor antagonists and the antinociception induced by U50,488H, κ agonist, given i.c.v. is blocked by nor-binaltorphine, but not by ε, μ, or δ opioid receptor antagonists.

β-Endorphin given i.c.v. releases Met-enkephalin which subsequently stimulated δ_2-opioid receptors in the spinal cord for the production of antinociception. This is evidenced by the finding that the i.c.v. administration of β-endorphin increased the immunoreactive Met-enkephalin in the spinal perfusates and intrathecal (i.t.) pretreatment with antiserum to Met-enkephalin, but not with antiserum to Leu-enkepahin, dynorphin A [1-17] or β-endorphin, blocked β-endorphin-induced antinociception. I.t. pretreatment with naltriben, a selective δ_2-receptor antagonist, but not other selective μ, δ_1, or κ receptor antagonists blocked i.c.v.-administered β-endorphin-induced antinociception. I.c.v. administration of morphine or DAMGO increases the release of noradrenaline and 5-HT and subsequently stimulation 5-HT receptors and α_2-adrenoceptors in the spinal cord for the production of antinociception. This contention is supported by the findings that i.t. pretreatment with DSP-4 and 5,7-DHT, which degenerates noradrenergic and serotonergic fibers respectively, blocked i.c.v. morphine , but not β-endorphin-induced antinociception. Also, i.t. pretreatment with 5-HT receptor antagonist, methysergide or α_2-adrenoceptor antagonist, yohimbine, blocked i.c.v. morphine-induced antinociception. I.c.v. administration induced by U50,488H or bremazocine releases 5-HT and dynorphin A [1-17] from the spinal cord for the production of antinociception. This contention is supported by the finding that i.t. pretreatment with antiserum to dynorphin A [1-17] or i.t. pretreatment with nor-binaltorphine or methysergide blocked i.c.v.-administered U50,488H or bremazocine-induced inhibition of the tail-flick response.

δ-, μ- and κ-opioid receptors have been cloned and their aminoacid sequences and the mRNA sequences for receptor protein synthesis have been determined. An antisense oligodeoxynucleotide is a short piece of synthetic DNA with a nucleotide sequence that is the reverse of and complementary to a part of a

mRNA. It therefore hybridizes to mRNA and inhibits the synthesis of the encoded protein. The antisense oligodeoxynucleotides were then utilized for characterizing the opioid receptor functions for antinociception.

I.t. pretreatment with δ_2-opioid receptor antisense oligodeoxynucleotide blocked the tail-flick inhibition induced by i.t.-administered δ-opioid receptor agonists, [D-Ala^2]deltorphin II, but not μ-, or κ-opioid receptor agonists, DAMGO or U50,488H. Likewise, i.t. pretreatment with μ-opioid receptor antisense oligodeoxynucleotide blocked the tail-flick response induced by i.t.-administered DAMGO or morphine, but not [D-Ala^2]deltorphin II or U50,488H. I.t. pretreatment with κ-opioid receptor antisense oligodeoxynucleotide blocked the antinociception induced by i.t.-administered U50,488H, but not DAMGO or [D-Ala^2]deltorphin II. It is concluded that the antinociception induced by selective μ-, δ-, or κ-opioid receptor agonists is mediated by the stimulation of respective μ-, δ-, or κ-opioid opioid receptors.

δ_2-Opioid receptor antisense oligodeoxynucleotide was also used to characterize the descending ε pain control system activated by i.c.v. administered β-endorphin. I.t, pretreatment with δ-opioid receptor antisense oligodeoxynucleotide selectively attenuated i.c.v.-administered β-endorphin-induced antinociception without any effect on the antinociception induced by μ-opioid receptor agonist, morphine or DAMGO, or κ-opioid receptor agonist, U50,488H. The results of the study confirm previous findings that the antinociception induced by β-endorphin is mediated by the stimulation of the δ_2-opioid receptor in the spinal cord.

At the supraspinanl sites, i.c.v. pretreatment with δ_2-antisense oligodeoxynucleotide attenuated [D-Ala^2]deltorphin II-, but not DAMGO-, β-endorphin or U50,488H-induced inhibition of the tail-flick response. Pretreatment with either δ_2- or μ-antisense oligodeoxynucleotide blocked the i.c.v.-administered morphine-induced inhibition of the tail-flick response, indicating that the antinociception induced by morphine given i.c.v. is mediated by the stimualtion of both μ and δ opioid receptors.

Besides β-endorphin which is a peptide, some opioid alkaloids process ε opioid receptor activity. Etorphine, a classical μ agonist, also process ε agonist activity. This is supported by the finding that antinociceptive response induced by etorphine given i.c.v. was blocked by i.c.v. administration of CTOP or β-

funaltrexamine and β-endorphin-[1-27], but not by ICI174,864 or nor - binaltorphine. On the other hand, the antinociception induced by i.c.v.-administered morphine was blocked by CTOP or β-funaltrexamine, but not by β-endorphin-[1-27], ICI 174,864 or nor- binaltorphine. The findings indicate that the antinociception induced by etorphine given i.c.v. is mediated by the stimulation of both μ and ε opioid receptors, whereas the antinociception induced by morphine given i.c.v. is mediated by the stimulation of μ, but not ε opioid receptors. Bremazocine, a benzomorphan κ agonist, also contains a component which is ε. This contention is supported by the findings that the inhibition of the tail-flick response induced by i.c.v.-administered bremazocine was blocked by both β-endorphin-[1-27] and nor-binaltorphine.

The inhibition of the tail-flick response induced i.c.v.-administered etorphine or bremazocine was blocked by i.t. pretreatment with antiserum to Met-enkephalin, but not with antiserum to Leu-enkephain β-endorphin or dynorphin A [1-17]. Desensitization of δ-opioid receptors in the spinal cord by i.t. pretreatment with Met-enkephalin, but not with Leu-enkephalin, or dynorphin A [1-17] attenuated i.c.v.-administered etorphine- or bremazocine-induced tail-flick inhibition. I.t. injection of ICI 174,864 antagonized i.c.v.-administered etorphine- or bremazocine-induced tail-flick inhibition. The findings indicate that antinociception induced by etorphine or bremazocine is mediated in part by the stimulation of ε opioid receptors at the supraspinal sites and by the release of Met-enkephalin which subsequently stimulates δ-opioid receptors in the spinal cord.

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Table 1 Pharmacology of Opioid Receptors

Opioid receptors	Endogenous ligands	Agonists	Antagonists
ε	β-Endorphin	β-Endorphin Etorphine Bremazocine	β-endorphin[1-27]
μ	?	Morphine DAMGO Etorphine	β-Funaltrexamine CTOP, naloxone
δ	[Met^5]enkephalin	DPDPE(δ1) Deltorphin II(δ2)	ICI174,864(δ1, δ2) BNTX(δ1) naltrindole(δ2>δ1) naltriben(δ2)
κ	Dynorphin A [1-17]	U50,488H Bremazocine	Nor-binaltorphine

がん疼痛緩和と医療用麻薬の適正使用について

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1．はじめに

がん疼痛緩和が，患者の毎日の生活と人生を考える上で大変重要な治療法であり，がんによる痛みを取ることができれば患者のＱＯＬ（Quality of Life: 生活の質）の改善に大きく役立つこと，さらにこうしたがん疼痛緩和にモルヒネ等の鎮痛薬の使用が大きく貢献することが，１９８６年のＷＨＯレポート（がんの痛みからの解放「Cancer Pain Relief」）により明らかとなった．以来，欧米先進諸国でモルヒネ等の鎮痛薬の使用が普及している．

我が国においても，ＷＨＯ方式がん疼痛治療法の内容を含めて，平成元年に厚生省・日本医師会が「がん末期医療に関するケアのマニュアル」を作成し，がん疼痛緩和治療について，その重要性と鎮痛薬を用いた治療について説明している．また，「がん患者の痛みに対するモルヒネの使い方マニュアル」や「医療機関における麻薬管理マニュアル」，「モルヒネ製剤の調剤マニュアル」も作成されており，病院や診療所においてモルヒネなどの麻薬を使う上で参考となっている．

ただ，こうした新しいがん疼痛治療法は，がんセンターや大学病院といった先進的医療機関では普及が進んでいるものの，それ以外の医療機関では必ずしも十分普及しているとは言えない現状にある．このためがん疼痛緩和と医療用麻薬の適正使用について理解と普及を促進する必要がある．

2．がん疼痛治療の現状とモルヒネの消費

ＷＨＯ方式がん疼痛治療法に従って鎮痛薬を使って治療すれば，９０％以上の患者さんの痛みは解決することが，一部の国で実証されているが，残念ながら日本の臨床の全体的な水準はまだそこまでいっていない．　日本の状況としては，厚生省がん研究助成金の研究で，１９８７年，１９９０年，１９９３年と３回にわたり，がんセンター，大学病院の痛みのあるがん患者を対象にした全国調査が行われた結果，除痛率は年々上がっているが半数程度ないしは半数以上が痛みが除去されず，不必要な痛みに苦しみつづけていることが示されており，除痛率の向上が望まれている．

モルヒネの消費量をみると，がん疼痛緩和治療の普及に伴い，ここ数年増加しており，平成６年の消費量は塩酸塩と硫酸塩を合わせて５５５ｋｇ（前年５０４ｋｇ）で１０％の増となっており，過去１０年の推移を見ると１１．８倍に増加している．

しかし，従来，我が国では，モルヒネが麻薬であるため，医療関係者の間において使用を抑える傾向にあり，単位人口当たりのモルヒネ消費量を比べてみると，カナダ，イギリス，アメリカ等欧米先進国の数分の一ないし十数分の一程度となっている．

3．モルヒネに対する誤解

モルヒネはがん疼痛治療に重要な役割を持つ医薬品であるが，「麻薬」であるため，患者，家族だけでなく，医師，看護婦等の医療関係者の間にも，麻薬中毒や依存性のイメージが強いこと等の理由から，モルヒネを使うことに抵抗感をもったり，痛み治療に必要な量の処方が進まないといったことがしばしば言われる．

こうした中毒や依存性の問題は，ＷＨＯ方式に従って患者に必要なだけのモルヒネを使用するかぎり問題とならないことは，すでにＷＨＯ方式を実践している病院で実証されている．

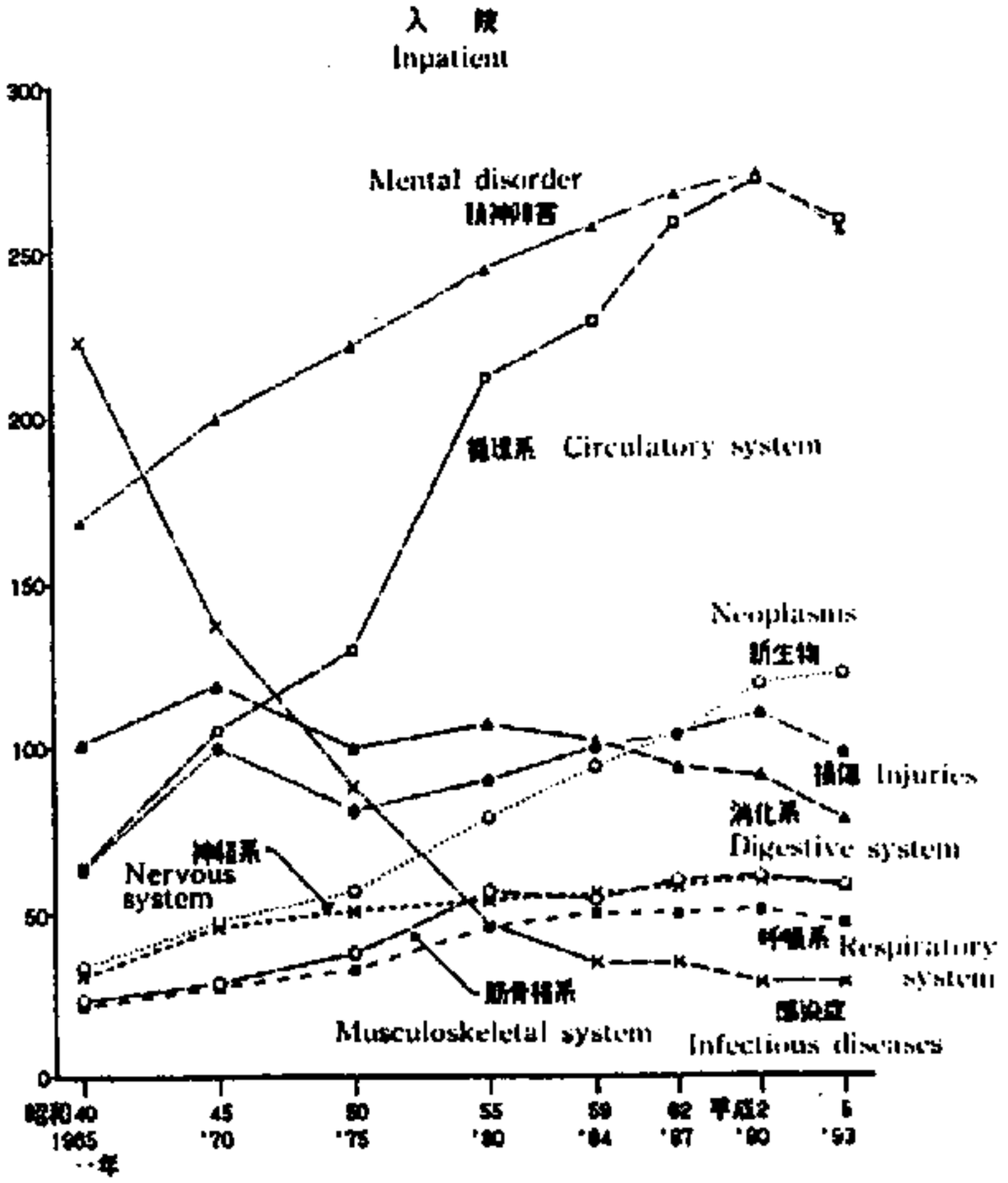
ただ，今日のようなモルヒネの徐放錠や持続皮下注射といった投与法は比較的新しいこと，モルヒネの鎮痛作用とともに生じる嘔気，便秘，眠気等の副作用対策が十分理解されていない場合があること，昔の麻薬中毒患者の印象が強烈であったこと，などから医療関係者においてもモルヒネ等の鎮痛薬を効果的に使いこなすには，ＷＨＯ方式がん疼痛治療法をよく学び，理解することが必要となる．

4．医療用麻薬の適正使用の推進

がん疼痛治療を普及し，患者が満足できる生活を送ることができるようにするため，モルヒネの鎮痛作用をうまく利用するための投与量と投与経路，モルヒネの使用に伴い生じる副作用対策，モルヒネが医療上の必要な使用だけに使われるように薬局等での管理を行うことなどについての理解が大切である．

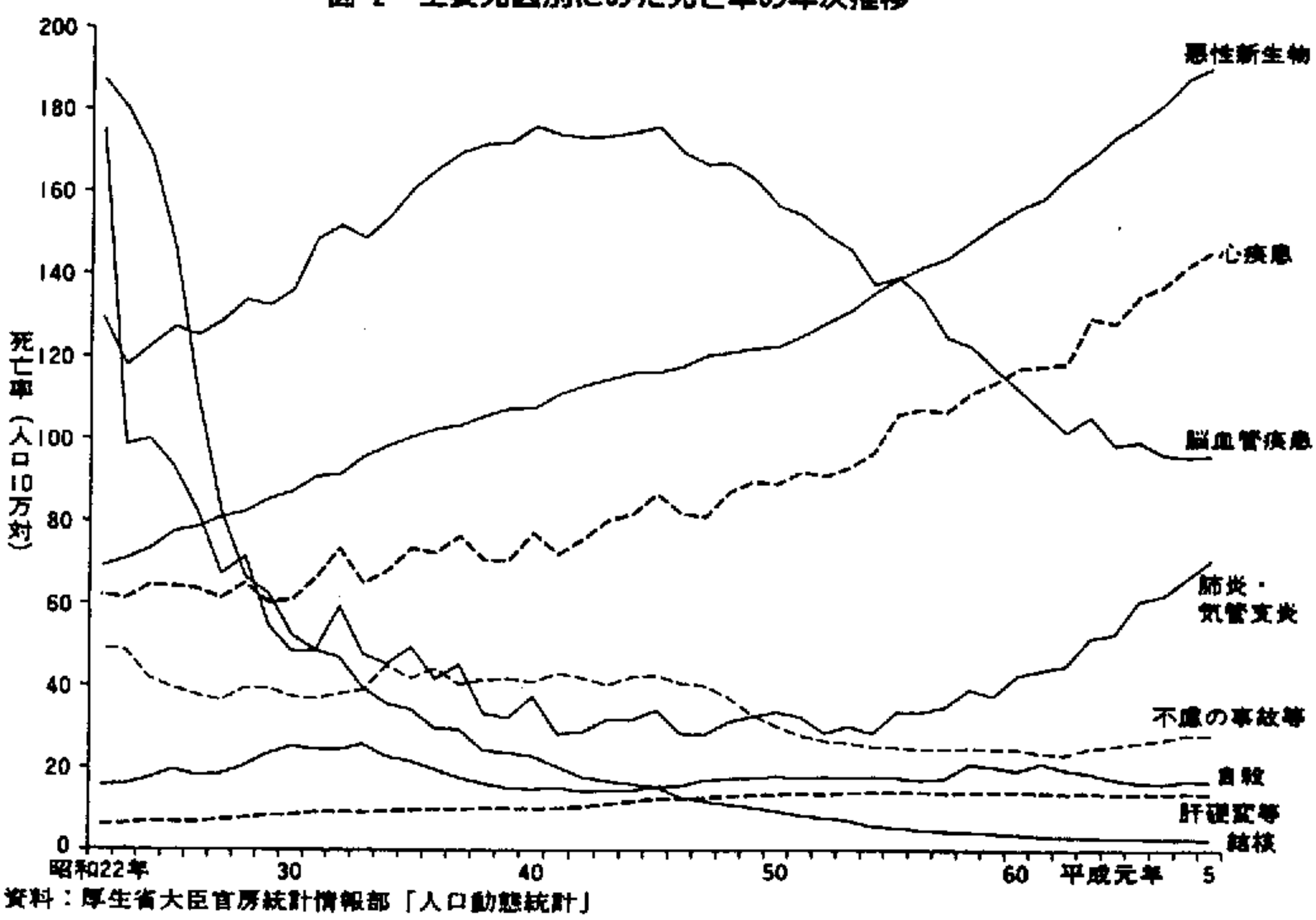
厚生省では，各都道府県を通じて，がん疼痛緩和と医療用麻薬の適正使用の推進につき周知に努めてきている．また，（財）麻薬・覚せい剤乱用防止センター等の主催で医療関係者向けの講習会も行われている．今後，医療の場において，全国的にがん疼痛治療法が普及し，患者の生活の質が向上することが期待される．

図 1　傷病分類別にみた受療率（人口10万対）の年次推移



資料：厚生省「患者調査」

図 2　主要死因別にみた死亡率の年次推移



資料：厚生省大臣官房統計情報部「人口動態統計」

表１　　あへんアルカロイド系麻薬の製造量及び消費量

品　　名	年	製造量(kg)	消費量(kg)
塩酸モルヒネ	58	52	40
	59	58	47
	60	60	55
	61	63	65
	62	88	79
	63	115	121
	元	154	93
	2	86	88
	3	104	102
	4	173	143
	5	96	180
	6	271	188
硫酸モルヒネ	58	—	—
	59	—	—
	60	—	—
	61	—	—
	62	—	—
	63	35	—
	元	181	89
	2	330	144
	3	469	190
	4	131	240
	5	299	324
	6	619	367

表２　　１日あたりのモルヒネ消費量（g）／100万人

（国際麻薬統制委員会の各年間統計による）

	1989	1990	1991	1992	1993
カ　ナ　ダ	41.9	50.1	56.6	61.1	67.3
イ　ギ　リ　ス	39.8	44.5	50.2	53.4	66.7
オーストラリア	24.1	31.0	34.8	40.3	58.9
ア　メ　リ　カ	19.6	24.0	28.2	33.6	40.2
フ　ラ　ン　ス	4.0	5.9	7.9	11.1	13.6
ド　イ　ツ	7.9	6.4	8.6	10.5	8.3
日　　本	1.9	2.5	3.2	4.2	5.3
ロ　シ　ア	2.7	2.3	2.3	5.0	2.5
イ　タ　リ　ア	2.3	2.7	—	2.8	2.4

＊当該年の直近過去５年の平均を表す。

＊遊離塩基に換算した数値である。